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THE JOURNAL

of

The Maine Medical Association

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Research in Maine Issue

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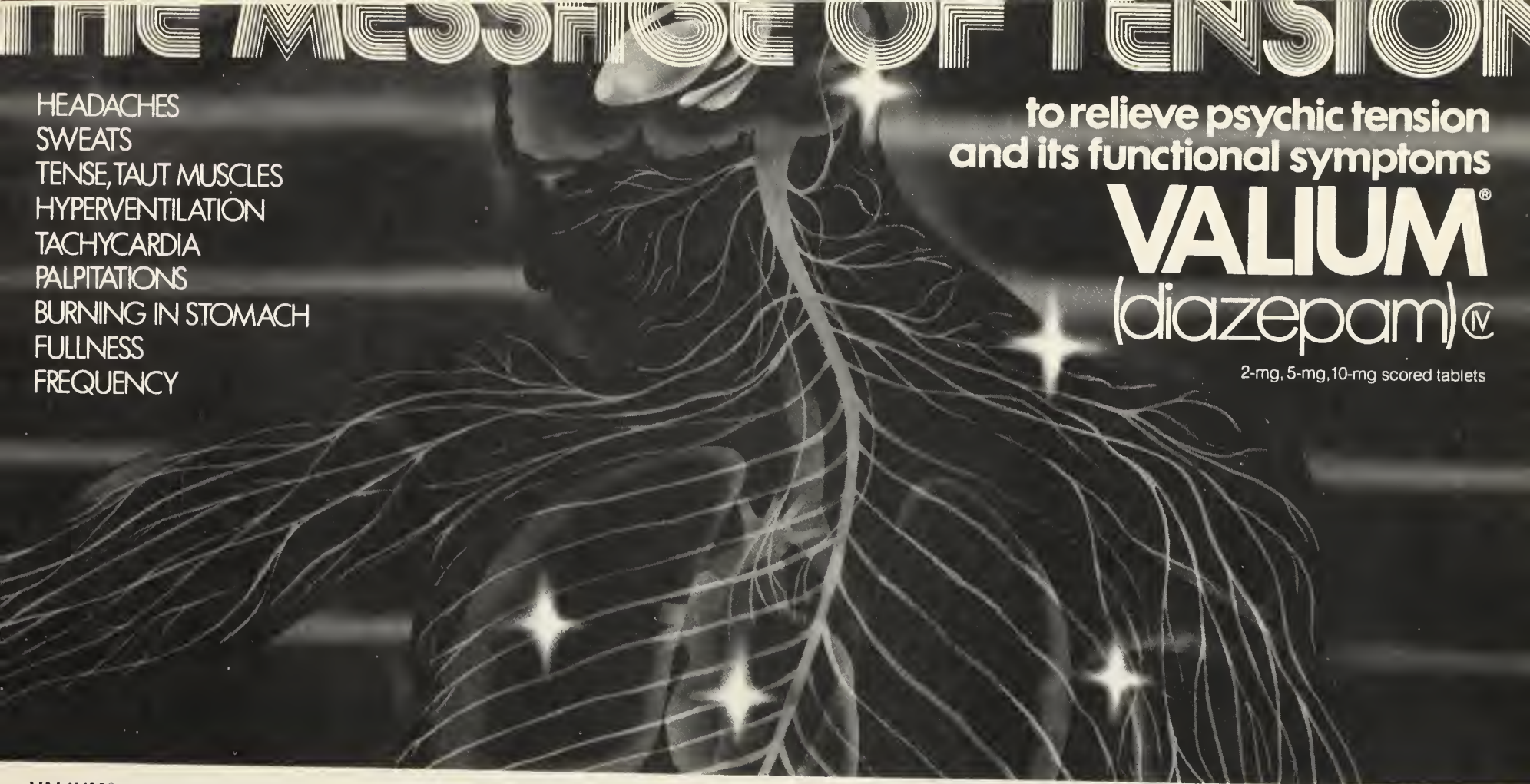
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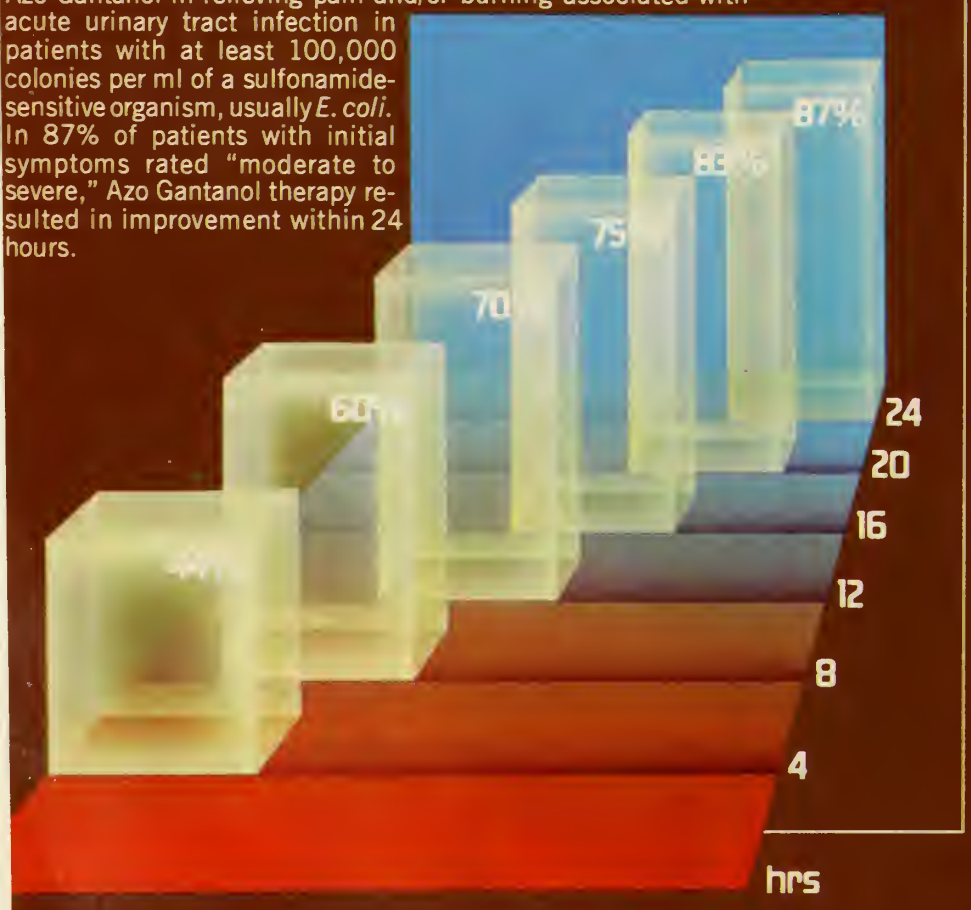
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Specific Proteins

I, The Immunoglobulins; II, The Complement Proteins; and III, The Lipoproteins

Robert F. Ritchie, M.D.*

Any discussion of plasma proteins is severely compromised by the rapid changes resulting from new studies. As a result, even general text books are deficient in clinically relevant information on the subject. The areas where change is bewildering are the immunoglobulins, the complement proteins and the lipoproteins.

Literally speaking, the body's framework and substance is protein. All tissues are proteinaceous, and the *metabolism* of endogenous organic and inorganic substances (e.g., lipids, carbohydrates, nucleic acids, steroids), as well as a wide variety of exogenous substances is mediated by individual proteins performing specific tasks. Specific functions, often reflecting an individual's genetic make-up, can now be measured through a variety of clinically applicable protein analyses involving such disciplines as hematology, immunology, nephrology, and even microbiology. This has fostered investigation at the molecular and submolecular level, culminating in the ability to study specific tissue proteins either in solution or in fixed tissue sections labeled by immunological reagents. Many of these studies are now used routinely in the medical subspecialties where the presence or distribution of a specific protein is important.

Several hundred proteins including coagulation factors, enzymes, immunoglobulins, and hormones, exist in human plasma (Ritzmann and Daniels, 1975) (Fig. 1, Fig. 2).

The purpose of this article is to assemble up-to-date clinical and laboratory information about these three sections beneath the general heading of specific proteins. Only these species in highest concentration or about which most is known are discussed (Table 1).

References of General Interest

Putnam, F.W. (ed.): The Plasma Proteins, 2nd edition, Vol. I, II, III, New York, Academic Press, 1975.

Ritzmann, S.E., and Daniels, J.C. (eds.): Serum Protein Abnormalities. Diagnostic and Clinical Aspects. Boston, Little Brown, 1975.

Henry, J.E. (ed.): Todd-Sanford, Clinical Diagnosis by Laboratory Methods. 15th edition, Philadelphia, W.B. Saunders Co., 1978.

I. The Immunoglobulins (Fudenberg, et al, 1976; Good and Fisher, 1971; Rose and Friedman, 1976)

This discussion will address only that portion of the immune system which is the hallmark of "bursa" dependency, the immunoglobulins. These soluble substances pass through the vascular spaces; some remain indefinitely, others become fixed to tissue surfaces, while still others enter body cavities functioning only briefly before being lost. IgG, the major immunoglobulin, moves through the body relatively freely, being found in all fluids and tissues. This is also true for other immunoglobulins whose molecular weights and sizes are similar (IgA, IgD and IgE). Normal IgM, on the other hand, is larger by a factor of 5 and is restricted almost entirely to the intravascular space. When modified by the incorporation of secretory component, IgM and IgA are actively directed to mucous surfaces.

The basic role of the immunoglobulins is to identify and "hit" a target identified as being foreign, including, at times, the organisms own products. When the "hits" per foreign particle or molecule exceed a critical threshold, other proteins are recruited that actually destroy or neutralize the antigen-bearing particle.

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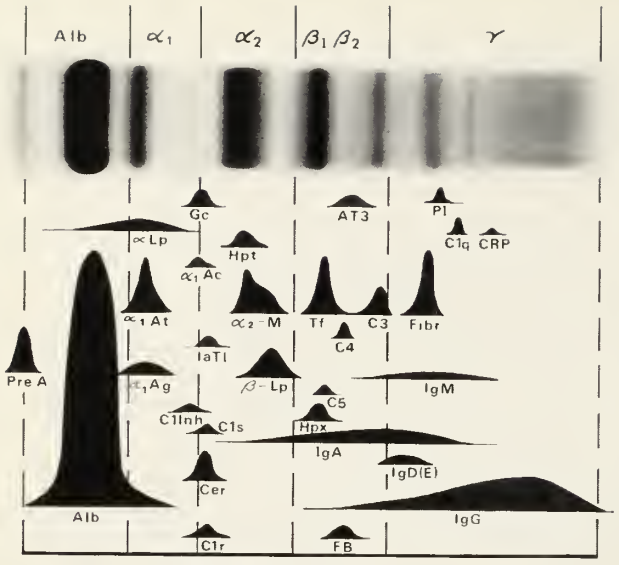


Fig. 1. Plasma protein electrophoresis pattern in agarose gel is composed of 5 fractions, each composed of many individual species (see Figure 2). Some of the major proteins are shown here in an artists rendition for clarity (adapted from Laurell, C.-B., Clin. Chem., *79*:99, 1973).

a_1Ac = Alpha$_1$-Antichymotrypsin
a_1Ag = Alpha$_1$-Acid Glycoprotein
a_1At = Alpha$_1$-Antitrypsin
a_2-M = Alpha$_2$-Macroglobulin
aLp = Alpha Lipoprotein
Alb = Albumin
AT3 = Antithrombin III
B-Lp = Beta Lipoprotein

Complement Components:

C1q, C1r, C1s, C3, C4, C5 = As designated
C1Inh = C1 Inhibitor
Cer = Ceruloplasmin
CRP = C-Reactive Protein
FB = Factor B
Fibr = Fibrinogen
Hpt = Haptoglobin
Hpx = Hemopexin

Immunoglobulins:

IgA, IgD, IgE, IgG, IgM = As designated

Pl = Plasminogen
Pre A = Prealbumin

The term "surveillance" has been repeatedly used to describe the primary role of the immune system. The word implies "continuously watchful" for the purpose of detection and "supervision or contact." The latter meaning is usually not considered as a function of surveillance, but is extremely apt in regards to the immune system. The organism's capacity to recognize foreign substances immunologically and to produce appropriate immunoglobulins against them is difficult to appreciate. Apparently receptors are available on specialized cells—the T lymphocytes—to receive these substances as though prescience were a quality of the immunologic organ. At times, as shown by experimental and clinical evidence, this cognitive system may be weak so that individuals or species react poorly to a particular antigen while others respond vigorously. It has been estimated that over 10^6 antigens are presented to the surveillance system during an individual's life span.

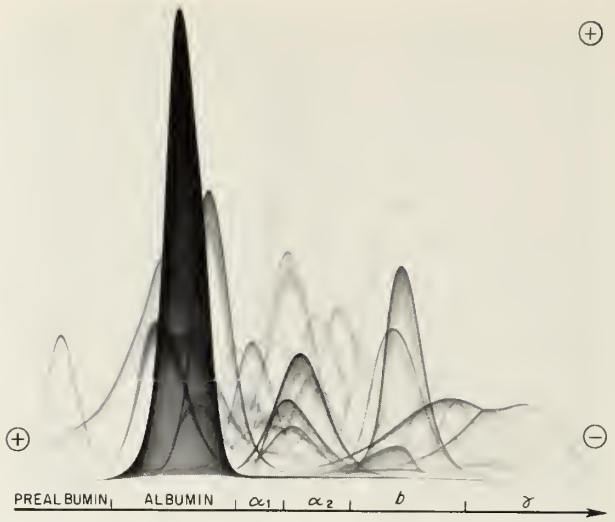


Fig. 2. Two-dimensional crossed immunoelectrophoresis in a gel containing high quality anti-whole human serum shows a complex population of proteins spread from prealbumin to gamma globulin. Each electrophoretic fraction can be seen to contain all or part of many individual species each identified as separate "rocket." The dense peak at the left is albumin and the broadest peak at the right is IgG. Without specific studies, it is impossible to unequivocally identify any of the others. (Plate courtesy of DAKOPATTES, A-F, DK-2000, Copenhagen, Denmark)

While certain functions are integral to an entire immunoglobulin class such as, for example, the virus neutralizing capability of IgM or the ability of secretory IgA to prevent bacterial colonization, the immunoglobulins generally serve as detectors or pointers upon which other nonimmunologic proteins act. Since immunoglobulins discriminate exquisitely, it is no surprise that our tissues are constantly being identified as non-self. The general attrition of activity and aging, exposure to relatively benign or ubiquitous agents such as dietary and environmental toxins, nonprescription drugs, alcohol, etc., alter the antigenic structure of tissue so that an antibody becomes bound to the surface. Since surveillance is an all or nothing phenomenon, some threshold mechanism must exist to prevent destruction of cells when a single epitope (the minimum immunogenic unit) signals a non-self state. Careful studies have shown that normal individuals have several dozen antibody molecules attached to the average red blood cell. But these cells live out their normal 120 day life span. The threshold is crossed when antibody molecules become attached in close proximity to one another. At that point, the sequence is activated which leads to cell destruction.

Animals reared in a germ free environment have markedly reduced immunoglobulin levels, and conversely individuals living in situations of poor personal hygiene and endemic parasitism have high levels of immunoglobulins. The circulating immunoglobulin level, therefore, reflects the intensity of stimulation of the producing cells—B lympho-

Table 1

Characteristics of Specific Proteins

Protein	Primary Site of Production	Normal Serum Ranges	# Variants / Subclasses	Deficiency State	Electrophoretic & Location	Molecular Weight
Prealbumin	Liver	0.1-0.4 g/l	?	Not recognized	Prealbumin	62,000
Albumin	Hepatocyte	3.2-5.5 g/l	20+	Yes	Albumin	66,248
Alpha$_1$-Lipoprotein	? Liver	3-7 g/l lipid + protein	?	Yes	Albumin-alpha$_1$	360,000
Gc-Globulin	Liver	?	2 (3)	Not recognized	alpha$_1$	51,000
Beta-Lipoproprotein	Liver	0.40-1.5 g/l	?	Yes	beta	380,000 (apoprotein)
Transferrin	Liver, RE System	2.0-3.4 g/l	21+	Yes	beta	76,500
Hemopexin	Hepatocyte	0.50-1.0 g/l	?	Not recognized	beta	60,000
Alpha$_1$-acid glycoprotein	Liver	0.35-1.40 g/l	2	Not recognized	alpha$_1$	40,000
Alpha$_1$-Antitrypsin	Liver	1.1-2.6 g/l	25+	Yes	alpha$_1$	54,000
Alpha$_1$-Antichymotrypsin	?	0.5 g/l	?	Not recognized	alpha$_1$	70,000
Inter-Alpha Trypsin Inhibitor	? Liver	0.2-0.7 g/l	?	Not recognized	alpha$_1$-alpha$_2$	170,000
Ceruloplasmin	Liver	0.15-0.45 g/l	5+	Yes	alpha$_2$	160,000
Antithrombin III	Liver	0.2-0.4 g/l	2	Yes	alpha$_2$	62,300
Haptoglobin	Liver	0.4-1.8 g/l	Many	Yes	alpha$_2$	100,000 (1-1) >100K (2-1, 2-2)
Alpha-$_2$ Macroglobulin	Liver	1.50-3.5 g/l age and sex dependant	?	?	alpha$_2$	820,000
Fibrinogen	Liver	1.8-4.2 g/l	Many	Yes	beta$_2$	340,000
Plasminogen	? Liver	0.1-0.25 g/l	?	Not recognized	beta$_2$	92,000
C-Reactive Protein	Liver	0.07-8.2 mg/l	Several	Not recognized	gamma	135,000
C1	Intestinal epithelium	C1q 1.80 g/l C1s 1.1 g/l C1r trace	?	Yes	q-alpha$_2$ s-alpha$_2$ r-beta	400,000 90,000 170,000
C1 Inhibitor	Liver and RE system	>0.11 g/l	? 2	Yes	alpha$_2$	90,000
C4	Liver/Macrophage	0.10->0.40 g/l	?	Not recognized	beta	200,000
C2	Macrophage	10-30 mg/l	?	Yes	beta$_1$	417,000
C3	Liver	0.90-2.30 mg/l	>20	Yes	beta$_1$	185,000
Factor B	Liver	0.15->0.60 g/l	4+	Yes	beta$_2$	94,000
Immunoglobulin A	Lymphoid Cells	0.4-3.5 g/l	2	Yes	beta-gamma	160,000 SIgA-400,000
Immunoglobulin D	Lymphoid Cells	10-400 mg/l	2	Yes	beta-gamma	180,000
Immunoglobulin E	Lymphoid Cells	50-600 ug/l	2	Yes	beta-gamma	180,000
Immunoglobulin G	Lymphoid Cells	7-15 g/l	4	Yes	alpha$_2$-gamma	150,000
Immunoglobulin M	Lymphoid Cells	0.25-2.0 g/l	? (2)	Yes	beta-gamma	850,000

cytes—by intrinsic or extrinsic antigens. A search for identity of the antigen(s) responsible for the dramatic increases seen in certain diseases of unknown etiology such as sarcoidosis, Sjogren's Syndrome, SLE, etc., has been a subject of great interest. Not unreasonably, these diseases have been considered as a response to endogenous antigen. As intriguing as the concept is, evidence remains elusive. It is known, however, that hyperimmunization with a specific antigen may result in massive hyperimmunoglobulinemia, only a fraction of which is specific antibody. The balance of the increase over preimmunization levels is not directed at the immunogen but represents increased levels of existing specific antibodies as well as immunoglobulins with no identifiable antigen. Some of this immunoglobulin production may well be the result of exposure to tissue protein altered by the immunization process itself. Inflammation, either localized as arthritis or abscess, or diffuse as in systemic rheumatic disorders, is also accompanied by nonspecific elevations of IgG, IgM and sometimes early in the process, IgA. The extent of the reaction and the ensuing hyperimmunoglobulinemia is modulated by many factors, among them age, sex, ethnic group (Prasad, et al, 1971), and genetic makeup (Allansmith, et al, 1968; Alarcon-Segovia and Fishbein, 1970; Baglioni, 1970).

Since the lymphatic organ is constantly reacting to stimuli, it is not surprising that the incidence of deviant or malignant cells lines is high (Kyle and Bayrd, 1976). The protein products of these abnormal cell lines or clones are homogeneous and show abnormalities of intramolecular structures sometimes including major deletions, e.g., Heavy chain and

Light chain disease. Whether the monoclonal protein represents an appropriate response to an as yet unidentified antigen remains unknown. Occasionally, modest levels of monoclonal protein appear during an infectious disease, rheumatic disorder or with epithelial malignancies only to vanish on resolution of the process.

One would not expect to find a monoclonal protein directed at a specific antigen since it results from undirected immunoglobulin production. However, several instances of monoclonal immunoglobulin production have been studied where specificity is directed at antigens not known to be pathogenic. Chronic immune stimulation not infrequently progresses from diffuse hyperimmunoglobulinemia to monoclonal immunoglobulin production as in amyloidosis. A suppressed immune response with reduced immunoglobulin levels gives rise to a series of monoclonal proteins during the resolution of the deficiency. This is dramatically seen in the congenital hypoimmunoglobulinemias after bone marrow restitution and also in patients following cessation of therapeutic immunosuppression, where small monoclonal bands are seen in electrophoresis. Eventually, many bands merge to form the normal immunoglobulin distribution after a sufficient number of clones have been stimulated.

Serum immunoglobulin levels in nonimmunological pathologic conditions reflect the basic process. When body surfaces are disrupted and fluid is lost as in thermal burns or protein losing enteropathy, all serum proteins are lost proportionally. If the protein loss is selective, as in the various degrees and forms of nephropathies, differential serum protein loss is observed. Classically, the severely nephrotic patient loses immunoglobulins G and A along with other smaller globulins, but IgM is retained and may become dramatically elevated due to its higher molecular weight.

The immunoglobulins are the primary means by which the body identifies that which is abnormal or not-self. Their presence throughout the body and the almost limitless flexibility of the cognitive and synthetic mechanisms are features apparently responsible for the plan's success since it has remained essentially unchanged for millions of years.

IMMUNOGLOBULIN A (IgA) (Mestecky and Lawton, 1973)

SYNONYM (Gamma-a Globulin, $Gamma_1$a-globulin, B_2A-GLOBULIN)

The immunoglobulin in second highest concentration is IgA. Perhaps because of its role in protecting mucous surfaces, its concentration in the population is extremely variable. Controversy still surrounds the relationship of serum IgA to the other immunoglobulins.

Concentration—At birth, serum IgA levels are undetectable by simple methods, reflecting low synthetic rates and the lack of placental transport. Adult levels are generally not attained until after the first or second year of life and sometimes much later. IgA levels in cord blood are usually less than 0.1 g/l. However, they may be markedly elevated as a result of contamination by maternal-fetal transfusion at the time of delivery. Infectious processes that elevate the cord serum level of IgM do not significantly elevate the level of IgA. Therefore, the comparison of IgM and IgA levels is necessary to attribute significance to an elevated IgM level. The combined elevation of IgA and IgM strongly suggests the presence of maternal blood in the sample. Adult IgA levels appear to vary irrespective of age, presumably being related to exposure to ingested or inhaled antigens.

Malnutrition, often related to socioeconomic level, significantly affects the levels of IgA by lowering secretory IgA (S-IgA) on mucosal surfaces and elevating levels in the serum (Sirisinha, et al, 1973). The increased incidence of chronic urinary tract infection among the poor relates to low secretory IgA levels. Acute pyogenic infections of the genitourinary tract are accompanied by increased levels of secretory IgA in the urine but not in the serum (Uehling and Steihm, 1971; Kaufman, et al, 1970).

Several careful studies have shown that serum IgA levels vary according to ethnic background and to geographic location, but existing information must be considered incomplete. Buckley and Dorsey (1971) showed that healthy, black American men had serum IgA levels about 20% higher than white men, that black women had levels about 25% higher than white women, that white men had 25% higher levels than white women and black men had levels 30% higher than black women (BM>WM>BF>WF). A few studies have shown that selected populations in different parts of the world show considerable variation in mean serum IgA values (Maddison, et al, 1975; Rowe, 1972). Countries such as Algeria and Chile have values 60% above those from Mexico (Alarcon-Segovia and Fishbein, 1970) and the Netherlands, while the U.S., Sweden and England have intermediate levels.

Infection with enteric pathogens results in a significant increase in serum IgA levels during convalescence (Waldman, et al, 1971). In addition, secretory IgA in serum and enteric fluids increases after infection (Wang and Fundenberg, 1973). Infections with viral agents might be expected to induce an IgA response since IgA exhibits viral neutralizing qualities. Careful studies showing a response are few, but it appears as though IgA responds variably to acute viral disease (LoGrippo, et al, 1968). Of interest is the fact that several diseases suspected of having a viral component have been associated with elevations of serum IgA, for instance, in juvenile and adult rheumatoid arthritis and in the early stages of SLE. Also, neoplasms of the lower GI tract and inflammatory bowel disease often are accompanied by significant serum IgA elevations.

Genetics—IgA molecules fall into two major

subclasses, IgA_1 and IgA_2, making up 82 and 18% of the total serum IgA respectively. The study of allotypes of IgA_2 in various populations has allowed interesting speculation on the evolution of plasma proteins in modern man (Wang and Fudenberg, 1973).

Physiology—IgA, like IgG, appears to be produced wherever lymphoid cells are found. However, unlike IgG, lymphoid tissue in close proximity to the GI tract is the principle source of intravascular IgA as well as the major source of secretory IgA (S-IgA). Stimulation of a specific IgA antibody by gut, respiratory or genitourinary tract associated cells is believed to occur most commonly as the result of oral ingestion of antigen. Parenteral immunization, in contrast, primarily produces an IgG antibody. S-IgA, in contrast to serum IgA, is a dimer, an assembly of two normal monomeric IgA molecules, attached through a small polypeptide chain—the 15,000 dalton J-chain—and the secretory component (SC, MWT-70,000). S-IgA is released into the lumen of the gut after polymerization with J-piece in plasma cells and secretory component produced by epithelial cells. The great bulk of this complex is found on mucosal surfaces, but small amounts of IgA coupled with SC can be shown in serum. Total IgA synthesis appears to be greater than that for IgG, with the bulk being transferred from the serum compartment, where it is in equilibrium, to the mucosal surfaces as S-IgA.

The majority of the literature on IgA focuses upon deficiencies. These deficiencies have been classified as follows: IgA completely absent, dysfunctional, deficient along with one or more immunoglobulins, or deficient with all other immunoglobulins normal. The deficiency may be either congenital or acquired (Hobbs, 1968; 1977). An appreciation of the association of IgA deficiency with serious disease is just beginning to evolve, primarily because testing of patients is still not widespread. Since S-IgA is responsible for the integrity of the mucosal barrier, it is not surprising that a variety of gastrointestinal complaints accompany absence of S-IgA (Trudeau and McGuigan, 1971). Malabsorption and sensitivity to certain foods are common but not invariable among patients lacking IgA. For an adequate evaluation of S-IgA, fluids from different organs, particularly those associated with clinical symptoms, are needed for study.

Increasing evidence indicates that patients lacking IgA have an increased incidence of malignancies, often involving the GI tract. Less frequently, IgA deficiency in children may be associated with ataxia telangiectasia (Ammann, et al, 1969). Perhaps of much greater importance to the population in general is transfusion reaction in the completely IgA deficient patient after receiving normal whole blood or plasma. The problem is of sufficient concern for the American Red Cross to study the incidence of deficiency in the donor population. IgA deficiency occurs with a prevalence of 0.5% in the U.S. (Dionne and Peoples, 1978).

As expected from the distribution of immunoglobulins in serum, the incidence of IgA monogammopathies is second only to that of IgG. Immunoglobulin associated with these disorders may appear either as whole IgA—either monomeric or polymeric or an admixture—or half molecules (Bernier, et al, 1977), or only the heavy or alpha chain. As laboratory technology has improved and the awareness of monogammopathies has spread, an increasing number of monoclonal IgA proteins of low concentration have been detected, representing either evolving or "benign" disease. By contrast, the majority of instances of high concentration monoclonal IgA proteins represent a manifestation of multiple myeloma. They are generally polymeric and often of sufficient concentration to produce hyperviscosity as severe as seen in Waldenström's macroglobulinemia.

The rare cases of alpha-chain disease (Seligman and Mihaesco, 1973) present in an unusual fashion both in the laboratory and in the clinic. The patients are often young, usually have gastrointestinal signs and symptoms, come from areas where parasitic and infectious disease are endemic, and have a broad IgA band on protein electrophoresis which, on further study, lack a light chain component. Surprisingly, these patients often improve with antibiotic therapy.

As an immunoglobulin, IgA plays a unique role in contributing major antibody protection to the mucous surface of the entire gastrointestinal, genitourinary and respiratory tracts. The long term viral neutralizing ability of S-IgA is best documented in oral polio immunization studies, where virus remains localized to the superficial mucosa, inducing S-IgA antibody production that prevents viral replication. Local exposure of gastrointestinal mucous surfaces to this type of antigen induces a purely local S-IgA response. On the other hand, viruses which extend beyond the mucous membrane or portal of entry to produce systemic infection induce circulating antibody of other immunoglobulin classes.

For successful bacterial colonization of hollow viscera, the organisms must be able to adhere to the mucosal surface. Specific antibacterial S-IgA antibody-binding to bacterial surface antigens inhibits adherence. Since S-IgA does not effectively bind complement, phagocytosis and killing of the coated and unaltered bacteria does not occur. The natural mechanisms for flushing the mucous surfaces prevent further bacterial build up that might exceed the local S-IgA ability to bind antigen. Of great interest is the possible use of the S-IgA system to prevent tooth decay resulting from cariogenic bacteria, primarily streptococcus mutans. Animal experiments suggest that oral immunization with live cariogenic bacteria can lessen the development of dental caries.

Persons lacking S-IgA often possess circulating IgG antibodies to ruminant proteins. S-IgA, directed against macromolecular antigens such as lactalbumin, bovine serum proteins, egg albumin, etc.,

apparently prevent the absorption of these proteins. Of speculative interest is the fact that because circulating IgA antibodies do not bind complement and therefore, do not produce toxic complexes, the IgA response may represent the safest antibody response (Hobbs, 1977).

IMMUNOGLOBULIN D (IgD)

SYNONYMS (Gamma-D Globulin)

Present in modest, but highly variable concentration, IgD remains an enigma in its role in the economy of the immune system. Although its structure clearly is that of an immunoglobulin (Rowe and Fahey, 1965a; 1965b), its performance either as a protective substance or as a mediator of disease has been elusive. Individuals with X-linked infantile hypogammaglobulinemia have low levels of IgD along with the other immunoglobulins.

Concentration—Few studies have been published documenting IgD concentrations in normal populations of various ages. A few points are clear. IgD is undetectable in the normal newborn or in cord samples not contaminated by maternal blood (Leslie, 1973). Detectable levels appear in most infants during the first year of life, but as in the adult, vary widely in concentration even when other immunoglobulins are in normal concentrations (Rowe, et al, 1968). Unlike the other immunoglobulins, IgD appears to increase in concentration during pregnancy.

Physiology—Human serum IgD appears to be present in two different subclasses (Rivat and Ropartz, 1971) produced in plasma cells in many areas of the body. Although cells close to the GI mucosal surface have been occasionally found to contain high IgD concentrations, the protein is not deteetable on the mucosal surface. The half-life of IgD is 2.8 days with ⅓ of the total mass being replaeed per day. This high turnover has been suggested as bearing some relationship to the extreme variability in serum IgD values.

Since the first case was reported in 1964 (Rowe and Fahey, 1965a), many cases of IgD multiple myeloma have been diseovered. In contrast to the other forms of monoelonal gammopathies, monoclonal IgD is almost always of the lambda light chain type.

The place of IgD in the body economy is unknown. However, the protein has been found in antibody populations directed against insulin, bovine proteins, penicillin, thyroglobulin, diphtheria toxoid and nuclear constituents. IgD deposits have been described in a small number of glomerulonephritis cases but, because large quantities of IgG have also been present, it has often been impossible to implieate IgD in the pathogenesis.

Analysis—Quantitation by gel diffusion plates is usually satisfaetory, but the need for a wide range of sensitivity and the often poor quality of antiserum have resulted in generally poor precision and aecuracy. The new methods of nephelometry yield excellent results over the required range. Since IgD myeloma frequently presents with low levels of monoclonal protein, the examining laboratory must eonsider such a disorder whenever abnormally low levels of other immunoglobulins appear in an adult sample even in the absence of a definite "M" component on electrophoresis. IgD should be tested in these circumstances. Immunoelectrophoresis or immunofixation can easily resolve the issue.

IMMUNOGLOBULIN E (IgE)

SYNONYMS (Gamma-E Globulin, Reaginic Antibody) (Ishizaka and Dayton, 1972)

The last immunoglobulin to be identified, IgE, plays the predominant role in the allergic response (Ishizaka and Ishizaka, 1967; 1971). This protein, present in low concentration in serum is also found on cireulating basophils and tissue mast cells.

Concentration—Immunoglobulin E levels appear to be genetically determined (Marsh, et al, 1974). In addition, molecules of IgE bear either of two antigenic determinants (e_1 and e_2). At birth, serum IgE levels approach the lower limit of routine RIA detectibility, i.e., 2-4 ng/ml. The mean level increases gradually in normal non-allergic children until about age 7-10 years, when the level approximates 100 ng/ml. The range is very wide in normal adults (70-1800 ng/ml). In allergic individuals serum IgE levels, with a few exceptions, are remarkably elevated, reflecting excess production of the protein. In areas where parasites such as ascaris and trichinella are endemic, serum IgE levels may rise as much as three orders of magnitude from the normal (Rosenberg, et al, 1971). IgE levels also may be extremely elevated in allergie pulmonary disease (Patterson, et al, 1973; Gerber, et al, 1971).

Physiology—Through the use of fluorescent antisera, plasma IgE producing cells have been found in surprising numbers. Individual plasma cells containing IgE are found in close proximity to the respiratory and GI tract (Gerber, et al, 1971). Germinal centers of lymph nodes in these areas also contain IgE producing cells, but spleen and bone marrow do not (Ishizaka and Ishizaka, 1971). The similarity between IgA and IgE production close to mucosal surfaces suggests that some link in function between the two is important in human well being. For years, IgE activity—that is, reaginic activity—was considered by immunologists and protein chemists to be a function of IgA, which itself suggests the similarities between the two proteins. Individuals with IgA deficiency and ataxia telangiectasia in addition are particularly prone to sinopulmonary infection (Ammann, et al, 1969). The lack of IgE, however, does not seem to predispose individuals to infection (Schwartz and Buckley, 1971). IgE is present in nasal and bronchial secretions of allergie individuals, but in proportion to serum or cell-associated IgE.

Several cases of IgE myeloma have been reported.

Doubtless others exist undetected as a result of unavailability of sophisticated testing methods. Both kappa and lambda light-chain types have been identified on IgE myeloma proteins. In massive polyclonal IgE elevations secondary to parasitic infestations allergic and atopic symptoms are commonly found (Patterson, et al, 1975).

Allergens are a group of substances that induce IgE antibody rather than of the other four immunoglobulin classes. Produced by plasma cells, the antibody molecules become associated with basophils and tissue mast cells via a cellular membrane receptor for the Fc portion of IgE. The bulk of cytotrophic IgE produced is free in the plasma and, if unassociated with membranes, remains only 12 to 24 hours. A host whose basophils have been sensitized with IgE directed at a specific allergen will react predictably when reexposed. The allergen will form a complex with basophil-bound IgE and, when two or more fixed IgE molecules become involved, a physical distortion of the cell surface will occur, releasing the chemical mediators of the allergic reaction, e.g., histamine, serotonin, SRS-A, and bradykinin. This results in increased vascular permeability bringing more cells and reactants into the area. In an individual previously exposed to an allergen, noncytotrophic IgG and IgM blocking antibodies also are available in the plasma and halt the progressive release of the vasoactive substances. Therapeutic desensitization is designed to foster the production of these circulating IgG and IgM blocking antibodies. In brief, the function of IgE is probably to stimulate repair of immunologically mediated tissue damage by the release of vasoactive substances from the sensitized basophils and mast cells. Why it is that the reaction becomes counterproductive in allergic and atopic individuals is unexplained and bears some similarity to autoimmunity.

When IgE antibody is produced by specific committed B lymphocytes directed against single antigenic determinants, as in the case of specific pollen allergies, a major portion of the total IgE may be directed to definable determinants (Gleich and Jacob, 1975). To induce IgE production requires the availability of uncommitted T cells. As with other immunoglobulins, thymectomized animals fail to synthesize adequate levels of IgE antibody despite the availability of uncommitted B cells. The synthesis of IgE antibody is not inhibited by the presence of IgG or IgM antibody to the same antigen. Individuals incapable of synthesizing adequate amounts of IgG, IgA, IgM or IgD, e.g., those with Wiskott-Aldrich Syndrome, Hodgkins Disease, or ataxia telangiectasia, have been shown to have high levels of IgE and exhibit allergy and eczema.

A handful of patients with high levels of monoclonal IgE have been studied. Relative to normal levels of IgE in plasma, these patients have levels 10^5 times higher. The presumed number of target cells for IgE being limited and approximately normal, the clinical expression of allergy in these individuals is no greater than for normal individuals, adding further support to the concept that only the cell-associated protein is of consequence or that the monoclonal protein is antibody directed at a clinically unimportant allergen. The fact that circulating levels of IgE may be extraordinarily high in allergic patients or individuals suffering from parasitic disease, and that these high levels appear to represent excess production of cytotrophic protein for which no receptor cell is available, could be interpreted as inappropriate production.

Analysis—Because of the low plasma levels, IgE cannot be quantitated by most commonly employed methods for serum protein quantification. Gel diffusion methods can be used to screen for extremely high levels of IgE ($>$1.5 ug/ml), but radioimmunoassay is required for measurement of most serum samples. As noted above, the serum fraction represents unused IgE, the balance being cell-associated. In light of this fact, the routine quantification of serum IgE is difficult to defend. Of importance, however, is the knowledge of the nature of the allergen. Tests have been devised whereby the antibody activity of the serum fraction can be measured giving the allergist specific information of therapeutic value.

IMMUNOGLOBULIN G (IgG)

SYNONYMS (Gamma Globulin, Gamma-G Globulin, 7S gamma globulin)

As the protein whose plasma concentration is normally second only to albumin, IgG makes up between 10 to 20% of the total intravascular plasma protein mass. Since IgG is the primary long term defense against foreign antigens, its concentration may vary widely as a result of socioeconomic, environmental and perhaps even genetic variables, none of which are at present taken into consideration when IgG blood levels are being interpreted.

Concentration—Perhaps the best understood variable affecting plasma IgG level is age. Fetal production begins in the second trimester of gestation, but attains only a small fraction of the eventual production capacity until late in the last trimester (Gitlin and Biacacci, 1969). IgG present in the fetus, therefore, is primarily of maternal origin, having been the only protein transported across the placental barrier. At birth, the synthetic mechanism responsible for IgG production is activated, presumably by the sudden exposure of the infant to the sea of antigens that make up the environment. The presence of maternal IgG affords passive immunity to the infant during the vulnerable few months after birth. Therefore, significant infection early in life generally results from exposure to agents unfamiliar to both the infant and mother.

Soon after birth, replacement of maternal IgG begins by the as yet poorly responding infantile humoral antibody apparatus. Consequently, there is

a sharp drop in serum levels to a nadir at the third to fourth month of life (Allansmith, et al, 1968). At the lowest point, when normal IgG values range between 3 and 6 g/l, protection against infectious agents is precarious but apparently adequate in the great majority of cases. Adults whose IgG levels have fallen to this range also rarely have infections indicating that, in general, 3 g/l is adequate to maintain protection against most infectious agents. Beyond 3 months of age, serum levels increase rapidly until about the eighteenth month of life, when near normal adult levels are attained. Since IgG is produced by committed B-cells present in the lymphatic tissues, it would be expected that, with age, IgG levels would rise with the continuing challenge from new or relatively new antigens. In fact, in a healthy adult population, IgG levels are stable.

Under ordinary conditions, the individual is being continually challenged with new and familiar antigens, resulting in IgG of many specificities being produced. The fact that many lymphoid cell lines are continually involved in production is reflected in the broad polyclonal electrophoretic distribution of IgG. Any sustained inflammatory or immunologic process results in measurable increase in the total mass of IgG, and massive elevations of polyclonal serum IgG can be seen. Serum levels in excess of 60 g/l have been observed in sarcoidosis, Sjogren's syndrome, osteomyelitis, disseminated tuberculosis, and some tropical parasitic infections. Levels in excess of 30 g/l may be seen in rheumatoid arthritis, systemic lupus erythematosis, chronic active hepatitis, advanced luetic infection—particularly of the congenital type, subacute bacterial endocarditis and in certain lymphoproliferative disorders. Intense stimulation may result in the development of small amounts of IgG with a monoclonal distribution. These oligoclonal bands, sometimes present in surprising numbers, are seen in viral hepatitis, sepsis, pyelonephritis, malignancies and SLE. With disease remission, these abnormal bands usually recede and disappear. Persistence can be viewed as a herald of chronic illness. Healthy people from areas where personal hygiene is less fastidious than American and West European cultures have higher average serum IgG levels. Relocation from an area of low socioeconomic standards to an area where the standard of living is higher results in lower IgG levels approaching but not quite reaching the new population mean. These studies, involving Africans and American blacks from economically depressed areas of the South, also showed that there was a significant difference in serum IgG levels between these groups and their matched counterparts in Great Britain and in the northern United States. Logically, therefore, IgG levels will be different but still normal for populations depending upon the intensity of exposure to immunogens (Higashi and Chowdhury, 1971). Diet may also play an important role in determining synthetic rates for IgG (Prasad, et al, 1971).

Continued on Page 13

Tenuate®
(diethylpropion hydrochloride NF)

Tenuate Dospan®
(diethylpropion hydrochloride NF) controlled-release

AVAILABLE ONLY ON PRESCRIPTION
Brief Summary
INDICATION: Tenuate and Tenuate Dospan are indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use such as those described below.
CONTRAINDICATIONS: Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result).
WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle, the patient should therefore be cautioned accordingly. *Drug Dependence*: Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy*: Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children*: Tenuate is not recommended for use in children under 12 years of age.
PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.
ADVERSE REACTIONS: *Cardiovascular*: Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System*: Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal*: Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic*: Urticaria, rash, ecchymosis, erythema. *Endocrine*: Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System*: Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous*: A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.
DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride): One 25 mg. tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg. tablet daily, swallowed whole, in midmorning. Tenuate is not recommended for use in children under 12 years of age.
OVERDOSAGE: Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phentolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product Information as of April, 1976
MERRELL-NATIONAL LABORATORIES Inc.
Cayey, Puerto Rico DD633
Direct Medical Inquiries to
MERRELL-NATIONAL LABORATORIES
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Cincinnati, Ohio 45215, U.S.A.

Licensor of Merrell®

References: 1. Citations available on request—Medical Research Department, MERRELL RESEARCH CENTER, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M.T., O'Dillon, R.H., and Leyland, H.M. A Comprehensive Review of Diethylpropion Hydrochloride. International Symposium on Central Mechanisms of Anorectic Drugs, Florence, Italy, Jan. 20-21, 1977.

Merrell

8-3921 (Y587A)

Whether overweight is a complicating factor... or just uncomplicated overweight.

Tenuate® Dospan® ℂ℣
(diethylpropion hydrochloride NF)
75 mg. controlled-release tablets



A useful short-term adjunct in an indicated weight loss program.

Overweight patients in certain diagnostic categories often require strict obesity control. Diethylpropion hydrochloride has been reported useful in obese patients with hypertension, symptomatic cardiovascular disease, or diabetes. While it is not suggested that Tenuate in any way reduces these complications in the overweight, it may have a useful place as a short-term adjunct in a prescribed dietary regimen. (Tenuate should not be administered to patients with severe hypertension; see additional Warnings and Precautions on the opposite page.)

In uncomplicated obesity.

Many patients, on the other hand, present with excess fat but no disease. While this condition is often termed uncomplicated obesity, complications of both a social and a psychologic nature may be distressingly real for the patients. In these cases, a short-term regimen of Tenuate can help reinforce your dietary counsel during the important early weeks of an indicated weight loss program.

Clinical effectiveness.

The anorexic effectiveness of diethylpropion hydrochloride is well documented. No less than 16 separate double-blind, placebo-controlled studies attest to its usefulness in daily practice.[1] And the unique chemistry of Tenuate provides "...anorexic potency with minimal overt central nervous system or cardiovascular stimulation."[2] Compared with the amphetamines, diethylpropion has minimal potential for abuse.

Tenuate—it makes sense. And it's responsible medicine.

Merrell

For prescribing information see opposite page



EMPIRIN® COMPOUND
with CODEINE

Each tablet contains: aspirin 227 mg, phenacetin 162 mg, and caffeine, 32 mg, plus codeine phosphate in one of the following strengths: #4—60 mg (gr 1), #3—30 mg (gr ½), #2—15 mg (gr ¼), and #1—7.5 mg (gr ⅛). (Warning—may be habit forming)

C III

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

It has become apparent that many drugs may affect serum immunoglobulin levels, sometimes in conjunction with clinical complications. In instances where a specific medication has been implicated, immunogobulin levels can be clearly associated with the administration of the agent. Antiarrhythmic doses of procaineamide, may, in certain individuals, produce a clinical disorder associated with dramatically elevated serum IgG levels (Kosowsky, et al, 1973). Administration of estrogens for contraception or replacement therapy are known to have significant effect upon the production of many globulins including IgG (Doe, et al, 1967; Song, et al, 1970). Other medications have also been linked with elevated IgG levels, but their temporal association with additional predisposing factors often makes the relationship unclear (Cushman and Grieco, 1970; Han, et al, 1969). The stimulation of the immune system by various chemicals (Cushman and Grieco, 1970) may represent an antigenic challenge with the small molecule acting as a hapten. The search for humoral antibodies to the individual agents, however, has not been rewarding.

Various conditions affecting the female reproductive tract have been associated with alterations in immunoglobulin levels. During pregnancy serum IgG values decrease progressively to between 81 and 87% of baseline levels (Maroulis, et al, 1971). In this study, values for black women were initially higher and fell less than their matched white counterparts. Significant diminution in IgG values is thought to parallel the fall in total protein secondary to the hydremia of pregnancy (Mendenhall, 1970). Women with an intrauterine contraceptive device (IUD) have been shown to have significantly elevated levels of serum IgG (Holub, et al, 1971). The mean IgG for subjects with an IUD was 60% higher than that of the control group, resulting in a mean value of almost 17 g/l and appearing to correlate with the length of time the device was in place.

Genetics—IgG polymorphism in man has been well established. Genetic control for this occurs in two locations, one on the heavy chain portion of the molecule (GM) and the other on the constant portion of the kappa light chain (INV) (Franklin, 1967; Baglioni, 1970). Significant deficiency in the absolute mass of total IgG is also clearly genetically controlled (Good and Fisher, 1971).

Physiology—The immunocompetent cell found throughout lymphoid tissues is the target of antigenic stimulation, responding by producing immunoglobulin molecules which are then released into the circulation and tissue spaces. Serum concentration reflects the balance between synthesis and destruction or loss. IgG production in spaces freely drained by the vascular tree, particularly the lymphatics, results in rapid equilibration. By contrast, production within areas where exit is restricted, such as the synovial or subarachnoid spaces, may give rise to disproportionately elevated IgG levels within those compartments. Production also may occur in close proximity to spaces draining to the outside, such as the kidney, producing elevated urinary levels of IgG not reflected in the serum.

IgG produced by abnormal cells can be divided into three categories: apparently normal molecules containing both H and L chains, partial deletions of either chain, and complete lack of either the H or L chain. Many, but not all such molecules are homogeneous as a result of their production by a single cell line or clone, hence the term monoclonal immunoglobulin or "M" component. This homogeneity is reflected most notably on serum protein electrophoresis. As electrophoretic technology has improved, individuals with low levels of monoclonal proteins are being identified. In contrast to the multiple myeloma patients with massive monocolonal IgG levels, individuals possessing small "M" components may have a wide variety of diseases including an indolent or "benign" monogammopathy, a lymphoproliferative disorder involving the B cell line, a carcinoma or sarcoma or an intense immunologic stimulus. This latter condition may produce more than one monoclonal band.

Most sera containing monoclonal IgG have individual protein molecules of a single L chain type—either kappa or lambda. Patients with oligoclonal IgG bands as a result of intense immunological stimulus, and an occasional patient with multiple myeloma may have more than one "M" band of different L chain types. A monogrammopathy may also appear only as the heavy chain. Each monoclonal IgG is further distinguished by its subclass and may be of any of the four subclasses: IgG_1, IgG_2, IgG_3 or IgG_4. The great majority of monoclonal IgG bands are of the IgG_1 subclass (77%), as would be expected from the percent of normal IgG_1 present in the serum of most individuas (70%). The percent of a given IgG subclass in "M" components versus its percent of total IgG in normal serum is: IgG_2 — 14%/25%, IgG_3 — 6%/6% and IgG_4 — 3%/3% (Shur, et al, 1974). The differing ability of these subclasses to fix complement would be expected to influence the clinical course of an immune-complex disease, but this appears not to be the case. At present, practical methods for IgG subclass characterization are not widely available.

Patients with high levels of monoclonal IgG may have significantly elevated serum and blood viscosity. If the protein is unpolymerized, a serum level above 45 g/l will produce the hyperviscosity syndrome. When polymerized, lower absolute IgG levels will result in altered blood flow. Even normal type immunoglobulins may exhibit peculiar properties at different temperatures. Cryoproteins, for instance, may occasionally precipitate and result in clinical complications. Appropriate IgG antibody production can occasionally result in soluble immune complexes when the circulating antibody and antigen reach a critical ratio. IgG involved in nonprecipitating circulating immune complexes makes up a substantial proportion of the cryoprecipitate

recovered from certain disease-related sera. IgG occasionally may also be extremely sensitive to changes in pH and ionic strength precipitating readily. Patients suffering from various gammopathies often release segments of whole immunoglobulins into the circulation. Free light chains (called Bence Jones' proteins if they exhibit the classic thermosolubility qualities), can often be found in the urine, and if renal failure has occurred, large amounts may be present in the serum as well. Occasionally patients will present with a plasma cell disorder that manifests with only the production of L chain. Perhaps the most common are those individuals who produce free light chain and whole myeloma proteins simultaneously.

The primary role of IgG is to bind to specific antigens. Once accomplished, and providing the antibody fixes complement, this combination sets the stage for the activation of the complement cascade, supplying the required conditions for immune-adherence, phagocytosis, and the release of vasoactive substances. In this manner, any foreign antigen recognized as having previously entered the body immediately becomes the target of an antigen/antibody reaction.

The great majority of antibodies serve to protect the host, but in certain instances, the response is counterproductive. For example, an IgG anti-hemophilic factor may neutralize the effect of Factor VIII concentrates administered to true hemophiliacs. Anti-tissue antibodies, stimulated by the release of brain, eye or testis antigens during injury may produce a self perpetuating, destructive autoimmune process. Occasionally, an IgG antibody will react against an individual's own tissue proteins, perhaps stimulated by foreign (particularly viral) proteins, complexed with normal tissue proteins. Common examples are the antinuclear factors of the IgG type. When the IgG—antigen reaction involves the complement cascade, immune-complex disease may result. Antigens such as streptococcal protein, hepatitis B antigen, carcinoembryonic antigen, parasitic surface proteins, DNA, and thyroglobulin to mention a few, have been implicated.

Low serum IgG levels can result from increased destruction as well as decreased production. Accelerated loss of IgG occurs in the protein losing syndromes involving gut or kidney as well as early in severe burns. Overwhelming sepsis and severe immunologic disorders such as SLE presumably remove IgG via immune complex formation. Low IgG levels due to the inherited disorders of the immune system are not uncommon, with levels ranging from near normal to virtually zero. Acquired deficiency of IgG often occurs in association with lymphoproliferative disorders such as multiple myeloma of the IgA type, Hodgkin's and other lymphomas, thymomas and other neoplasms (Hermans, et al, 1976). Administration of cytotoxic agents may also result in marked reduction in serum IgG levels.

Analysis—IgG can be easily analyzed in most cases. Its high concentration allows simple tests to perform well, e.g., radial immunodiffusion, immunoelectrophoresis, immunofixation, nephelometry, and turbidimetry. IgG and its four subclasses react well with antiserum made against the Fc piece of normal human IgG. However, in cases where either polymerization or the production of partial molecules has occurred assay will yield incorrect values if the method is dependent on diffusion rate. Radial immunodiffusion will yield falsely low values for polymerized IgG and falsely high values for the incomplete IgG of heavy chain disease. Other techniques, particularly nephelometry, are less bothered by this problem. Electrophoresis has traditionally been used to measure serum IgG, which is the primary component of the gamma fraction. However, because a sizeable portion of the total IgG migrates beneath the beta-globulin area, serious errors may occur. Newer quantitative techniques are resulting in decreased emphasis being placed on IgG electrophoretic quantitation. Electrophoresis remains important for the qualitative evaluation of monogammopathies.

IMMUNOGLOBULIN M (IgM)

SYNONYMS (Gamma-M Globulin, Beta$_2$-M, 19S Gammaglobulin)

IgM has the highest molecular weight of all immunoglobulins.

Concentration—Like the other immunoglobulins, serum concentrations at birth are markedly depressed. Normal newborns have serum IgM levels not exceeding 0.1-0.2 g/l. Soon after delivery IgM production increases, so that by the end of the first year, nearly adult levels are present (Buckley and Dorsey, 1971). Cord blood from infants infected by viruses or spirochetes in utero may have markedly elevated IgM levels (Alford, 1971). However, interpretation of the findings must take into account the possibility of transplacental transfusion of maternal blood or contamination of the cord sample by maternal blood during collection. To minimize the chance of this error, a simultaneous IgA measurement is necessary. IgA is not produced by the infected fetus but is in relatively high concentration in maternal blood. An elevated IgA level suggests the presence of maternal blood in the sample, while an elevated IgM level without elevated IgA suggests intrauterine infection. This is not to say that both situations cannot occur simultaneously. Maternal blood contamination could go undetected in the instance of an IgA deficient mother. Ideally, some other protein marker to indicate maternal blood would be desirable: for example, the pregnancy-associated macroglobulin or SP3 globulin, which is normally absent from cord blood.

Selective deficiency of IgM is uncommon beyond the first few weeks of life. Soon after birth, IgM production rapidly increases serum IgM to adult levels. Patients lacking IgM are susceptible to pyogenic organisms (Yocum, et al, 1976), and have increased

incidence of Hodgkins lymphoma and celiac disease. Later in life, normal individuals have serum IgM concentrations between 0.3 and 2.0 gm/l. IgM values may fall in the later decades (Buckley and Dorsey, 1971; Maddison, et al, 1975). Gender plays an insignificant role early and late in life, but, during the childbearing years, mean serum IgM values may differ by as much as 25% to 30%; higher for white females as compared to white males. Black men have up to threefold higher IgM values than black women in the fourth to sixth decades of life, but in the third and fourth decades black women have IgM values 50% higher than black men.

IgM levels, like IgG levels, react to factors related to socioeconomic level, e.g., personal hygiene, diet and infection. Invasive parasites may markedly elevate serum IgM levels.

Pregnancy and contraceptive medication appears to have little effect upon the level of IgM (Laurell, et al, 1970; Mendenhall, 1970). There has, however, been an unsubstantiated impression that, in certain women on contraceptive medication, IgM levels do climb returning to pretreatment levels on discontinuation of the medication. Mean values serum IgM from Nigeria are over threefold higher than from Mexico, while United States and British levels are about twofold higher than Mexican. Identification of an ethnic component as being responsible for serum IgM regulation is extremely difficult, since diet, personal hygiene, and invasive parasites as well as other factors all influence IgM levels.

Genetics—When studied with antisera prepared against single monoclonal IgM proteins, IgM shows heterogeneity (Franklin and Frangione, 1967). Two structural and antigenic subclasses of IgM have been demonstrated but this polymorphism as a reflection of genetic control has not been proven. Chromosomal abberations have been described in patients with IgM macroglobulinemia, and there is a single report of IgM macroglobulinemia in twins. Seligmann and co-workers (1967) studied families of patients with IgM monoclonal proteins and found a significant number with abnormalities in IgM metabolism.

Physiology—IgM is the product of antigen stimulated immunocompetent cells throughout the body. The IgM response to an unfamiliar antigen is quicker than for other immunoglobulins, but unlike IgA, the IgM antibody synthetic apparatus appears to retain no immunologic memory. The IgM producing cells appear scattered throughout the bone marrow, lymph nodes and spleen and often resemble transitional forms between lymphocytes and plasma cells. Maneuvers to correct the resulting hyperviscosity syndrome often fail to lower circulating IgM levels despite the removal of a liter of plasma per day. Plasmaphoresis, however, does lower the plasma viscosity.

IgM contains J-chain, and like dimeric IgA, can associate with secretory component and be released onto mucous surfaces as protective antibody. In certain patients deficient in S-IgA, S-IgM is present. It plays a major protective role in the gut in IgA deficient patients who also lack S-IgA. S-IgM, like S-IgA, is stabilized by the presence of the secretory component, presumably to insure its survival in the relatively hostile environment of the gut or GU tract.

Synthesis of IgM can assume three abnormal forms. 1) 7S polyclonal monomers rather than 19S pentamers, 2) monoclonal pentamer or monomer or 3) u-chains where only the heavy chain of IgM is released without associated light chains. Waldenström's macroglobulinemia refers to a disorder with high levels of 19S monoclonal IgM. These patients may be seriously threatened by high serum viscosity producing IgM protein precipitation in extremities and chilled areas. Patients with a variety of disorders including rheumatoid arthritis, lymphoproliferative disorders and macroglobulinemia of the 19S type also have significant levels of monomeric or 7S IgM. In some instances, 7S monomer may predominate.

Elevated polyclonal IgM accompanies many infections or inflammatory disorders. Furthermore, processes resulting in damage to the liver parenchyma are almost always accompanied by elevated levels of polyclonal IgM. IgM is the first immunoglobulin to respond to an antigenic stimulus, and markedly elevated levels generally indicate chronic longstanding disease. Dramatic levels of polyclonal IgM may be seen in biliary cirrhosis, chronic active hepatitis, active sarcoidosis, various lymphoproliferative disorders, and with systemic parasites. More modest levels—2 to 4 times normal—occur in rheumatoid arthritis, active hepatitis, a host of serious and benign viral disorders, and neoplasia. Often associated with increases in the circulating mass of IgM are molecules with specific biochemical characteristics, such as rheumatoid factor, cold agglutinins, anti-mitochondrial antibodies and cryoglobulins. These functional groups of IgM contribute little to the absolute IgM mass in spite of their high titre of activity.

IgM plays a major role in the protection against gram negative bacteria. Perhaps the best known IgM antibodies are the rheumatoid factors. These have been studied extensively for the allotypic specificities and for their relationship to various immunologic disorders, particularly those involving immune complexes. Anti-blood group substances, anti-I or-i cold acting antibodies, heterophile or Forssman and Wasserman antibodies, and a substantial portion of the antinuclear antibodies are of the IgM class.

Analysis—Routine analysis for IgM presents the greatest number of pitfalls of the common plasma proteins. Quality assurance programs have repeatedly shown that quantitation of IgM by clinical laboratories, usually by RID, varies unacceptably. There are several reasons. Perhaps of greatest concern has been the variable specificity and affinity of anti-IgM antisera available commercially. Analysis of a sample containing high levels of IgM may fail to produce a precipitin reaction, leading to the er-

roneous impression that IgM is absent. Furthermore, IgM, because of its size and ability to complex with other proteins, may migrate through gels at variable rates, seriously affecting quantitative analysis. Significant amounts of 7S IgM in a sample compared against a normal 19S IgM reference serum will yield values considerably at variance with the expected value, with the 7S containing samples yielding a much higher result.

Electrophoresis of macroglobulinemic serum is frequently complicated by the susceptibility of the "M" protein to precipitation when dissolved in alkaline buffers of low ionic strength. Electrophoresis in the cold also may prevent movement of the protein by the production of an immovable gel or precipitate. Confirming the presence of free u chain requires techniques other than immunoelectrophoresis. Immunofixation, where antiserum and antigen are brought into almost immediate contact after electrophoresis circumvents this problem. Small IgM bands, often seen in patients afflicted with various neoplasms, also require immunofixation for their characterization. The quantitative analysis of IgM is best accomplished in a free liquid by light-scattering or nephelometry. Techniques which are affected by molecular size and configuration, such as the diffusion-in-gel methods, do not perform well in tests for IgM, whereas nephelometric methods yield more accurate results regardless of molecular size.

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II. Complement Proteins (Ruddy, et al, 1972; Alper, 1974; Polly and Bearn, 1975; Tucker and Nakamura, 1975)

Unlike other groups of proteins, the complement proteins are an orchestrated family with each member tied either functionally or antigenically to the others. Nine of these proteins, labelled numerically C1-C9, have been identified. In simplest terms, the complement proteins link the antigen- antibody reaction to the inflammatory response. Once a cell or molecule has been identified as abnormal by the presence of bound antibody, and the density of these bound immunoglobulins has reached a certain threshold, the cascade of complement activation begins and leads to their ultimate removal or destruction.

Several aspects of complement action require integrity of the entire sequence; others, once the system is activated, act independently. The lysis of bacteria or red blood cells requires the entire chain of C1-C9. However, preparation of a bacterium for immune adherence and phagocytosis requires only the enzymatic cleavage of C3 to produce fixed C3b, a protein that can apparently act alone to stimulate phagocyte activity.

Complement activation occurs via two pathways; the classical and the alternative. Both have the same C3-C9 sequence but are initiated differently in the early phase, one being triggered by antibody, the other by a variety of intrinsic and extrinsic substances not involving antibody. In either case the key action of complement is amplification at each step with recruitment of other proteins and cellular elements.

The circulating complement proteins ordinarily lie dormant but have such an explosive and self perpetuating capability that without some form of control, the host would be destroyed. At several points in the cascade inhibitors exist that prevent runaway activation of the subsequent steps. Where C1 esterase inhibitor is deficient, for example, minor incidents trigger an escalating syndrome, called heriditary angioedema, that can result in death.

The complement proteins also participate in the acute phase proteins. Difficulty in interpreting complement protein assays quantitatively is compounded by their susceptibility to simultaneous stimulation of production and consumption. Furthermore, a normal immunochemical concentration does not rule out pathology, since the protein may be converted. For this reason, some workers perform the assay for total hemolytic complement along with immunochemical quantification.

C1

SYNONYM ($C^1$1)

The first element of the complement system to become activated in the classical, i.e., antibody initiated sequence, is the large and complex calcium dependent molecule, C1. It is made up of three immunologically distinct subcomponents, C1q, C1r, and C1s, each with a clearly defined function.

Concentration—C1 and its subcomponents are produced early in gestation, with adult levels being reached at about the time of birth. No information is yet available about the effect of pregnancy or contraceptive medications on C1 synthesis.

Genetics—Each of the subcomponents have occasionally been found deficient in individual patients. C1r deficiency in siblings has been reported, but there is little other evidence to indicate a possible mode of inheritance (Marden, et al, 1976; Moncada, et al, 1972).

Physiology—Several workers have shown that the complete C1 molecule is a product of intestinal columnar epithelial cells. The fact that C1 contains three quite different subcomponents brings up the possibility that each subcomponent may be synthesized separately and assembled in a common site. The occurrence of individual subcomponent deficiencies

provides evidence for such a possibility. Fibroblasts and tumor cells have been shown to produce C1s and spleen cells to produce C1r in vitro.

The whole C1 molecule circulates as an inactive protein maintained intact by the presence of the calcium ion. Since the surfaces of normal human red blood cells often bear small numbers of antibody molecules, it might be expected that activation of the complement system with the resultant cell destruction would be a common occurrence. C1 activation, however, requires that complement fixing antibody molecules be within a certain distance of one another before C1 can bind, as well as availability of multivalent antibody and antigen. When the conditions are met for C1 activation, the C1q portion first binds to the Fc portion of an antibody. C1q is a six-armed structure capable of attaching to six particle-bound antibody molecules. Following this attachment, C1r acquires the capability to activate the third portion of C1, C1s. C1s, enzymatically modified by C1r, itself becomes enzymatically active and cleaves C4. C1 activation requires the availability of intact C1 and calcium ions.

Analysis—Immunochemical analysis of C1 subunits can be accomplished with specific antiserum in the presence of suitable buffers containing calcium binding (chelating) agents, allowing the whole serum molecule to disassociate into its three subunits. C1q and C1s have been analyzed successfully in light-scattering and gel diffusion systems; C1r only by gel diffusion. The ability of C1q to bind to immune complexes has been exploited in clinical assays.

C1 INHIBITOR (C1INH) (Frank, et al, 1976)

SYNONYMS (C1s-Inhibitor, C1-Inactivator, C1-Esterase Inhibitor, Alpha$_2$-neuroaminoglycoprotein)

Perhaps the most dramatic disorder related to the proteins involved in the complement system is the life threatening disorder called hereditary angioneurotic edema (HANE or HAE). Localized swelling, often following minimal trauma or emotional stress, can affect the skin, GI or GU tract as well as the upper airway. The latter gives rise to obstruction, requiring prompt surgical intervention.

Concentration—The clinical syndrome of HANE is transmitted as an autosomal dominant trait, heterozygotes being affected. The homozygous deficiency state may represent a lethal condition. Variable genetic defects are suggested by the fact that 15 to 25% of HANE patients have a functional deficiency of C1INH but normal or even supranormal serum concentrations.

Physiology—C1INH, normally produced in hepatocytes, cannot be demonstrated in liver tissue from genetically deficient individuals in spite of serum levels of 10% of normal. Small amounts of the protein may be synthesized also in cells of the reticuloendothelium system and in fibroblasts.

The activation of C1 and the release of C1s can be accomplished by reaction with surface-bound antibody and by proteolytic factors such as plasmin or products of the clotting system such as Hagcman factor. The action of C1s on its natural substrates C2 and C4 is normally held in check by the inhibitory effect of C1INH. Therefore, in patients deficient in functional C1INH, there will be activation of C2 and C4 with a local release of vasoactive peptides, believed to be responsible for the painless, usually non-pruritic, edema of HANE.

Analysis—C1INH can be analyzed functionally or immunochemically. The functional test is based upon the protein's ability to block the hydrolysis of N-acetyl-tyrosine ethyl ester by C1s. It is clear from the preceding discussion that the functional assay is important. Immunochemical analysis can be performed by gel diffusion, electroimmunoassay, immunoelectrophoresis and by nephelometry.

C4

SYNONYMS (C^{1}4, Beta $_{1e}$ Globulin)

Numbered out of sequence in complement activation, C4 is actually the second step in the process. It has the second highest serum concentration of the nine complement proteins.

Concentration—Little is known about the effects of socioeconomic level, diet, medications, pregnancy, etc., on C4 levels. There appears to be little change from birth to old age (Adinolfi, et al, 1968). Since values range widely in a population, interpretation of serum levels is difficult unless values are extremely low (<0.10 g/l).

Genetics—A suspicion that C4 structure, as demonstrated by electrophoretic polymorphism, does reflect genetic control has existed for some time. However, no simple inheritance pattern has been described (Rosenfield, et al, 1969). Genetic C4 deficienty has been identified in man and in animals; it appears to have little effect upon health.

Physiology—Free in the circulation, C4 remains inactive until modified by the esterase, C1s. The product of this reaction is a small fragment liberated from one of the three C4 chains. Cleavage of this polypeptide exposes a binding site, making possible the further reaction of activated C4 with activated C1 and the subsequent release of another small fragment, C4a. Activated C4 released into the fluid phase is rapidly degraded by proteolytic enzymes. It appears, therefore, that the meaningful consumption of C4 occurs only at the site of cell or tissue bound antibody and C1. C4a alters vascular permeability in a fashion similar to that of other anaphylaxotoxic substances. It is also capable of virus neutralization. The remainder, C4b, complexed with C1, forms a precursor for the next step in the complement cascade: action upon another plasma protein, C2. C4b which does not become bound to C1 rapidly becomes incapable of further reaction.

In various pathologic states C4 levels may be ex-

tremely low, indicating activation of the classical complement pathway. Normal C4 levels in the presence of significantly depressed C3 levels suggest that the alternative pathway is active. In many instances, both classical and alternative pathways may be activated simultaneously. Because C4 may bind to particles in analytical samples such as chylomicrons, care should be taken to document, by more than one technique, low serum C4 levels. Markedly elevated values of C4 are occasionally observed in apparently healthy individuals. C4 levels increase in response to an acute inflammatory process, further complicating the interpretation of C4 values in the presence of immunologic diseases that may be accompanied by inflammation. It is, strictly speaking, an acute phase reactant in addition to being a complement protein.

Analysis—Immunochemical analysis in gels or in nephelometric systems requires that the antiserum be directed at the stable portion of the molecule. Problems in quantitating C4 nephelometrically can arise in a chylous sample; the protein may falsely appear to be absent or in low concentration. Under such circumstances, gel techniques may demonstrate normal levels. Centrifugation will show C4 to be in the lipid layer. The failure of the rapid nephelometric systems to detect the protein suggests that antigenic determinants are masked and require hours before steric changes allow a precipitation reaction to occur. In agarose electrophoresis, the C4 band is not ordinarily visible, unless developed by immunofixation to show a broad area in the beta zone.

C2

SYNONYM (C'2)

C2 is of particular interest to investigators because of its genetic implications and its role in certain well established clinical syndromes. It is involved in the third major step of the classical complement pathway through production of the C42 complex (C3 convertase) by activated C1, i.e. C1s.

Concentration—Homozygous deficiency of C2 in several kindreds has been reported (Osterland, et al, 1975; Kim, et al, 1977). Heterozygotes have one-half normal serum C2 levels. The prevalence of the recessive gene is of the order of 1% in the population, predicting the incidence of the homozygous state as approximately 0.01%. The HLA system and C2 have been reported to be genetically associated (Wolski, et al, 1975).

Physiology—C2 is synthesized by monocytes in man and released into tissue spaces and into the circulation (Colten and Frank, 1972). Enzymatic cleavage of C2 by activated C1 in the presence of magnesium ion produces two products, C2a and C2b. This action can occur on cell surfaces, in proximity to bound antibody, and also in the fluid phase. C2a, combined with the previous complex of antibody and portions of C1 and C4, produces the complex C142a (or EAC142) also known as C3 convertase that is rapidly inactivated unless C3 is available. The residue, C2b, has not been isolated and may be rapidly degraded by the further action of C1s.

In addition to being found in healthy individuals, several apparently normal family members of patients with a systemic lupus-like syndrome have been shown to be C2 deficient. These individuals, clinically indistinguishable from SLE patients with normal levels of C2, possess a variety of autoantibodies as do their kindred. C2 deficienty has been reported in association with dermatomyosytis, hereditary angioneurotic edema and vasculitis.

Analysis—C2 may be analyzed functionally or immunochemically. In hereditary angioedema, C2 is absent by functional assays, but present by immunochemical and electrophoretic methods. Gel diffusion methods work well in experienced hands. C2 is a relatively poor antigen, presumably because of its high sugar content, and therefore, does not precipitate well in gels. Staining the gels improves visibility.

C3

SYNONYMS (B_{1A}, B_{1C}, C'3)

Of the large number of plasma proteins integral to the complement cascade, C3 is in highest concentration. Its relationship to disease and its biochemistry have been the most extensively studied. Although it is primarily a complement protein, it also is an acute phase reactant, a feature which demands care for adequate interpretation.

Concentration—Production in the fetus begins in the first trimester, and none is transported across the placenta. At birth, mean values in cord blood are about 50% of the normal adult, attaining full concentration within a few weeks. Very little is known about the effect of pregnancy or contraceptive medications on C3 levels. One study suggests that a small increment occurs with withdrawal of contraceptive medications (Laurell, et al, 1970).

Genetics (Alper and Rosen, 1974)—Like many other plasma proteins, C3 exhibits genetic polymorphism, best demonstrated on prolonged electrophoresis in agarose gel. The two most common alleles are the S and F (slow and fast) inherited as an autosomal condominant trait. However, there are over 20 different alleles. These common variations appear to have no effect on health. The discovery of a kindred with almost complete deficiency of C3 indicates that absolute levels of C3 may be under genetic control and inherited as an autosomal recessive with expression also in the heterozygote.

Physiology—The position of C3 in the complement cascade is such that its activation results via either the classical and/or alternative pathways. It, therefore, plays a key role. In the presence of the C42 complex, C3 is cleaved enzymatically to produce a small fragment, C3a and C3b. C3a, an anaphylatoxin, induces smooth muscle contraction and increased vascular permeability to substances such as plasma

proteins. C3a degranulates tissue mast cells, thus releasing histamine leading to smooth muscle contraction and altered vascular permeability. C3b, bound to cell surfaces, promotes immune adherence and opsonization of foreign particles.

In the alternative pathway or the properdin system, C3 is cleaved by the complex C3bBb (rather than by C42) to produce C3a and C3b. The generation of C3b by Factor B results in the recruitment of additional activated Factor B, a phenomenon without parallel in the classical pathway.

In any system capable of propagating a potent, even toxic sequence of events, governors must be available. The step involving C3 is limited by the presence of a serum protein, C3 inactivator (C3INA) acting in the presence of at least one other globulin, B_{1H}, that further splits C3b, regardless of its method of production, into the stable inactive protein core, C3c and also an inactive protein C3d.

Inadequate levels of a protein having such a key position in the body's protective mechanism must result in profound alteration in the host's ability to resist infection. Individuals with severe primary C3 hypocomplementemia—less than 1% of normal levels—have such problems. Secondary C3 hypocomplementemia is generally not associated with decreased protection against infections. Processes that involve immune complex production or the reaction of circulating antibody with solid antigen (e.g., red blood cells or bacteria) result in variably low serum C3 levels, ranging from marked to subtle. The latter may be detectable only by multivariant analysis utilizing a variety of other serum protein measurements (Pinsker, 1978). Some of the most dramatic C3 depressions occur in acute glomerulonephritis, membranoproliferative glomerulonephritis, and systemic lupus erthymatosus where serum levels may fall to 0.2 grams per litre (Grieco, et al, 1971). Significant reductions also occur in chronic active hepatitis.

Analysis—Since native C3 degrades readily to the inactive form by destruction of a portion of the molecule, immunoanalysis must be directed against the stable C3c portion of the molecule. Attention to immune reagent specificity is paramount. Passive gel diffusion methods are adversely affected by molecular weight changes in vitro but electroimmunoassay, nephelometry, and fluorescent assays are not. The functional assays of C3 require careful sample handling to prevent loss of activity in vitro.

In agarose gel electrophoresis with CA^{++} or Mg^{++} containing buffers, the band of native C3 can be clearly seen in the slow beta region, and if degradation occurs, a faster moving fraction becomes prominent near transferrin in the fast beta zone.

FACTOR B (Alper, 1974)

SYNONYMS (C3PA, C3 Proactivator, GBG, Beta$_2$-glycoprotein II)

The properdin system, of which Factor B is a prominent member, was identified years before its true role in alternative pathway complement activation was proven. For a long time its very existence was seriously questioned. Now that the alternative complement pathway has been defined, only Factor B has been found in sufficient concentration to warrant consideration in this chapter. Factor B, a glycine-rich beta-globulin (GBG), allows entry into the common sequence of complement activation from the alternative pathway.

Concentration—Levels in cord serum average 120mg/L, rising to adult concentrations by three months of age. At the end of the third trimester, maternal serum levels peak at 420 mg/l.

Genetics—Factor B demonstrates genetically controlled polymorphism. The major types consist of F (fast) and S (slow) with several infrequent subtypes. F_1 occurs primarily in blacks and S_1 in Caucasians. The gene frequencies in black and whites are 0.437 and 0.709 for F and 0.512 and 0.278 for S respectively. There appears to be no functional or clinical significance for the different phenotypes. Control of Factor B, C2 and C4 is closely linked to the major histocompatibility locus on the sixth chromosome in man.

Physiology—Factor B's major role is the enzymatic cleavage of C3 to form C3a and C3b, analogous to the action of C42 in the classical pathway. Factor B itself is activated enzymatically by Factor D (GBGase, C3Pase) in the presence of magnesium ions and C3b to produce two fragments: Bb (glycine-rich gamma-glycoprotein, GGG), and Ba (glycine-rich alpha-glycoprotein, GAG).

Analysis—Factor B degrades to subunits about half as large as the native molecule, having major implications in gel-diffusion immunoanalysis. The alpha (GAG) and gamma (GGG) fractions can confuse the gel pattern when aged serum or plasma is examined. Assays performed in liquid, e.g., nephelometry, provide the most reliable quantitative measurement. After prolonged electrophoresis and immunofixation with antiserum to Factor B (GBG), breakdown products as well as molecular variants can be visualized. In immunoelectrophoresis, Factor B and its two major breakdown products will produce three distinct arcs.

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III. The Lipoproteins

ALPHA$_1$-LIPOPROTEIN (LpA)

SYNONYMS (High Density Lipoprotein, HDL Protein, Alpha$_1$-lipoprotein)

Of little interest since its discovery except as in some way related to liver disease and a rare deficiency state, LpA has come to be regarded as a potential indicator of vulnerability to cardiovascular disease, more specific than previously recognized parameters (Olsson and Carlson, 1975; Glueck, et al, 1976; Castelli, et al, 1977; Gordon, et al, 1977). Unfortunately most publications describe only the lipid content of LpA (HDL) without including the protein base although a direct relationship exists between the cholesterol and protein content for LpA.

Concentration—At birth, full term babies have about 75% of normal adult levels of LpA. Premature babies have a significantly lower level. Babies born at less than 33 weeks gestation have LpA values close to 50% of adult values. Levels in preterm infants rise rapidly to the expected term levels but change only gradually thereafter (Ginsburg and Zetterstrom, 1977).

Women have significantly higher LpA cholesterol than men; rising at puberty, peaking in the fourth decade and falling gradually thereafter. No information is available on the effect of pregnancy and contraceptives on LpA levels. Data has been presented indicating that physical activity increases LpA (cholesterol) levels while heavy smoking depresses plasma levels.

Genetics (Fredrickson, 1973)—The defect called Tangier disease is named after the island community in the Chesapeake Bay, Maryland on the U.S. East Coast where it was first discovered (Hoffman and Fredrickson, 1965). The incidence in the population is approximately 1 per 100,000 and all patients described thus far have been Caucasian. Patients with the disorder have been reported from other parts of the world, but it remains a rare syndrome. Careful biochemical studies reveal that normal LpA is missing from the serum of the Tangier disease patient but protein immunologically identical to LpA$_1$ and LpA$_2$ are present in an abnormal ratio at levels less than 1% of expected (Assmann, et al, 1977; Curry, et al, 1976). The disease is manifested by large concentrations of cholesterol esters in various tissues such as the spleen, liver, lymphoid tissues (particularly and most dramatically in the pharyngeal tonsils), and rectal mucosa. Lipid deposits in the cornea also have been reported. Neurologic abnormalities more common in adults include sensory and motor deficits. A relapsing, peripheral neuropathy in adolescence has been reported. Homozygous individuals have yellowish-orange deposits of lipid in the tissues. Heterozygotes are normal clinically, but possess cholesterol values less than 1.25 g/l and low levels of LpA.

The genetics of LpA associated with cardiovascular disease has not been elucidated, but several authors have described familiar associations. It might be expected from current data that accelerated arteriolosclerotic heart disease would occur in heterozygous individuals as well as the homozygous (Miller, et al, 1977).

Pathophysiology—In vitro studies indicate that LpA's function is to carry lipids in a fashion similar to other lipoproteins. A distinction, however, is that the triglycerides are scantily present in LpA. Levels of cholesterol and phospholipids are almost equal. The route of cholesterol traffic is out of the vascular tissues. In addition, the protein inhibits the uptake by vascular smooth muscle cells of cholesterol laden LDL protein from the circulation.

Analysis—Measurement by radialimmunodifussion, electroimmunoassay and radioimmunoassay have been successful. The protein is labile during isolation, but its stability in patient samples is unknown.

BETA-LIPOPROTEIN (LpB)

The majority of lipid circulating in the blood is

complexed with two major groups of proteins. While there are several classification schemes, the simplest is to divide them into two major groups of high- and low-density molecules as defined in the ultracentrifuge. The low-density group is the primary carrier of cholesterol, triglyceride, phospholipids and fat soluble vitamins and because of the association of lipids and cardiovascular disease interest in the transport mechanism has been great, but in general, centered about the transported moieties rather than the carrier proteins themselves (Frederickson, et al, 1967; Scanu, et al, 1975; Fisher and Truitt, 1976).

Since specific protein analysis, as addressed in this text, is oriented toward the practical rather than the research point of view, the discussion to follow will focus upon the proteins that bear the B antigenic determinants, e.g., chylomicrons, VLDL and LDL or the family of Beta-Lipoproteins (Schoenfeld, et al, 1974; Gotto, et al, 1972).

Concentration—Mean cord serum levels of LpB are approximately 40% of normal adult values regardless of sex (Leonard, et al, 1976). By the end of the first year, serum values reach 80% of adult levels and climb again at the time of puberty. A general population will show an increasing number of elevated values after the age of puberty. Upper range values in ambulatory, presumably well, individuals are reached in the 6th decade, to decline into the 9th decade toward juvenile levels. Lower range values of approximately 0.4 g/l remain unchanged throughout life. Dividing the population by sex does not alter the results.

Hyperlipidemia and hyperlipoproteinemia may occur in certain individuals while taking oral contraceptives (Sachs and Wolfman, 1971). Increased triglyceride levels have been noted as a result of alcohol ingestion, and even with modest intake, a susceptible individual may experience elevations of LpB (Ginsburg, et al, 1974). Cessation of alcohol ingestion results in a prompt fall in serum lipids and a slower reduction in the levels of carrier protein. Exercise is known to lower serum lipids and has also been shown to lower the levels of LpB. Chronic ingestion of large amounts of fats as commonly practiced in parts of the southern U.S., can markedly increase LpB levels independent of obesity.

Genetics—Several aspects of LpB metabolism are under genetic control. Two major structural systems have been described, a complex system termed Ag and a simpler one, Lp. Clinical significance to the genetic variations has been slight with individuals possessing the Lp(—) phenotype having lower LpB values than those that are Lp(+) (Giblett, 1969).

Deficiency or absence of LpB has been described where the deficiency is accompanied by clinical signs and symptoms. Congenital abetalipoproteinemia results in neuromuscular disorders, retinitis pigmentosa, bizarre arthroses, growth retardation, and malabsorption generally manifesting in childhood. Inheritance as an autosomal recessive with variable penetrance has been proposed. Several cases described in the literature occurred in consanguineous marriages. The homozygous deficient patients often present various clinical aspects of the syndrome while the heterozygous parents have reduced LpB levels but no associated signs or symptoms (van Buchem, et al, 1966).

Hyperlipoproteinemia is fairly common, however, the sporadic cases as well as those occurring within a familial setting can be difficult to confirm as a manifestation of a genetic disorder rather than of exogenus or pathogenic origin (Brown and Goldstein, 1976). Hyperchylomicronemia of the familial Type I, is believed to be homozygous for a rare mutant gene. Hypercholesterolemia of the Type II familial variety, is fairly common in North America and is characterized by lipid deposits in a variety of tissues, premature cardiovascular disease and extreme elevations of cholesterol and LpB. Studies of families exhibiting the familial type of hypercholesterolemia suggests that it is an autosomal dominant trait and will be expressed in the heterozygous state. A single parent, therefore, will be expected to affect half the offspring, however, penetrance is variable and expression of the disorder may be difficult to ascertain. Individuals with Type III hyperlipoproteinemia do occur in families but the incidence suggests that the mode of transmission is not related to a single gene. Type IV hyperlipoproteinemia has been difficult to attribute to a genetic defect; however, familial instances do rarely occur, suggesting that some form of inheritance is sometimes involved. Individuals with the Type V abnormality similarly have familial instances of disordered lipid metabolism, but the occurrence in relatives of the Type IV disorder has suggested that perhaps both types represent various expressions of the same genetic disorder. Completely normal individuals are distinctly in the minority in these family studies.

Pathophysiology—Synthesized by the liver, serum levels in part reflect demand for transport of endogenous or exogenous lipid. The primary role of the LpB is to carry glycerides, cholesterol, phospholipids, carotonoids, and fat soluble vitamins to and from the gut, liver, fat and tissues which metabolize lipid in association with LpB (chylomicrons, Beta (LDL) and prebeta (VLDL) lipoproteins).

Exogenous glycerides absorbed through the gut are reassembled in the intestinal cell as chylomicrons to be transported via the lymphatics to the general circulation. Within 5 to 10 minutes, in the fasted individual, chylomicrons are cleared from the circulation mainly by the liver. When large amounts of fat are present in the diet, adipose tissue plays an important role in the clearing of chylomicrons. Endogenous glycerides synthesized in the liver are transported by the prebeta or very low density lipoproteins to tissue sites where hydrolysis of glycerides occur producing free fatty acids. Small amounts of dietary cholesterol absorbed from the gut enters the circulation along with glycerides in

chylomicrons, but the majority of cholestrol is synthesized de novo by many tissues, entering the interorgan traffic in the beta-lipoprotein fraction or LDL. Phospholipids are transported in each of the LpB classes.

Carotenoids and fat soluble vitamins A, D, E and K enter the circulation in chylomicrons. After metabolism of these particles, vitamin A (retinol) becomes associated with the retinol-binding protein and pre-albumin while vitamin D becomes associated with the vitamin D-binding or Gc globulin. The beta lipoproteins also contain some of the vitamins.

Loss of small molecular weight proteins through the damaged globerulous results in retention of large molecular weight species including LpB. Hepatic production, perhaps stimulated by loss of small molecular weight species, is increased and is reflected as a marked elevation of LpB in conditions such as the nephrotic syndrome where serum levels can exceed 5 g/l. Elevations also may accompany sepsis, pancreatitis, chronic liver disease and acute alcoholism.

Analysis—Because of the physicochemical characteristics of the LpB associated proteins, a great many publications have dealt with isolation and analysis. Capitalizing on the flotation ability of lipids, ultracentrifugation has been used to divide the lipoproteins into classes. The method has been limited by its expense and has not found a place in general medicine. Separation of classes by their precipitability by dextrans and various metal salts also has not been widely adopted. The light-scattering ability of the particles after they have been sorted by differential filtration through membranes has only been sporadically used. The most widely employed technique has been electrophoresis where the various classes migrate as individual bands in the medium and can be grossly quantified after staining with fat soluble dyes. The method reached wide use in the 1970's, but because of the lack of standardization between methods and various separation media, reported results were frequently unsatisfactory from a clinical point of view. Utilization at present continues to decline.

Immunochemical determination appears to have considerable potential now that methods for analysis have been developed that are not affected by differences in molecular weights that has such a marked affect upon the gel diffusion methods. Analysis of total LpB by nephelometry is a useful and accurate method.

Biochemistry—The three fractions that contain LpB protein—chylomicrons, beta-, and prebeta-lipoproteins, are composed of a protein structure and various amounts of lipid. Chylomicrons contain only 0.5-2.5% protein. The prebeta or very-low-density fraction (VLDL) contain a protein immunochemically different from apo B, apo C (MWT 834,000 daltons (Brown, et al, 1969). Apo B has a molecular configuration made up of several repeating units believed to be approximately 380,000 daltons.

Depending upon the electrophoretic method used, patterns stained for proteins show considerable variation in the location of the individual beta lipoprotein fractions. In argarose gel, the beta fraction frequently appears as an irregular band in variable locations depending upon the concentration.

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A Low-Cost, Accurate, Integrated-Circuit Vector Lead System*

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We have been using a vector lead system consisting of three rows of eight electrodes around the thorax plus a foot-head lead[1]. Resistor networks were used to solve the Gabor-Nelson equations[2] for dipole moment. In that system, the following equations were developed:

$$M_x = G_x k HP V_x \quad (1)$$
$$M_y = k S V_y \quad (2)$$
$$M_z = G_z k HP V_z \quad (3)$$

where M_x, M_y, M_z = X, Y, Z components of the spatial dipole moment (heart-vector), M, and V_x, V_y, V_z = output voltages from the resistor networks. H, P and S are thoracic height, periphery and cross-sectional area, respectively; k = thoracic conductivity and G_x and G_z are factors which depend on the shape of the thorax cross section and the attenuation of the resistor networks. There were three output cables from the networks which gave the voltages V_x, V_y and V_z. These voltages were applied to Grass P511 amplifiers. The amplifier output voltages could then be recorded directly or applied to an X-Y recorder for obtaining vector loops.

We have recently revised the system to use integrated circuit (IC) components, resulting in a reduction in size of the amplifiers and simpler operation. The objective of this paper is to give the new circuits and the method of derivation. The basic equation for M_x is as follows[1]:

$$M_x = \frac{k HP}{32}\left\{\Sigma (V_7 - V_3) + \cos\theta \left[\Sigma(V_6 + V_8) - \Sigma(V_2 + V_4)\right]\right\} = \frac{k HP}{32} V_x \quad (4)$$

In the ellipse used to represent the thorax cross-section, electrode 1 is at the center of the back, #5 at the midsternal line and #3 and #7 at right and left mid-axillary lines, respectively. Electrodes #2, 4, 6 and 8 are midway between the other electrodes. The electrodes can be applied visually with sufficient accuracy. The Σ sign in equation 4 means that the potentials from corresponding electrodes on the three levels are added together.

Figure 1 shows the M_x circuit. The amplifiers are integrated circuit (IC) "Instrumentation Amplifiers". The overall dimensions of the amplifier used (Burr-Brown 3629BM) including lead wires are 20.3 x 12.7 x 9.7 mm. Fourteen pin sockets are available for these amplifiers. The IC instrumentation amplifier is similar to an operational amplifier, except that gain is determined by a single external resistor, rather than by the ratio of feedback to input resistance. Amplifier gain can thus be controlled by a single potentiometer.

Summations between the different electrodes are done by fixed 500,000 ohm (500K) resistors. Thus, in Figure 1, there are three 500K resistors connected to the positive input terminal of amplifier #1. The other ends of these resistors connect to electrode #7 on the three levels. Similarly, three 500K resistors connect from the negative input of amplifier #1 to electrode #3 on the three levels on the thorax. The output of amplifier #1 is then proportional to the first term in equation 4.

The second term in equation 4 is solved by amplifier #2 and multiplier #1. In this case there are six 500K resistors connected to each input terminal of amplifier #2. The output of amplifier #2 goes to one input of multiplier #1 (Burr-Brown 4206J). The other input to multiplier #1 comes from potentiometer R1, which is adjusted in proportion to cos θ. (The determination of cos θ will be discussed below).

The output of amplifier #1 and multiplier #1 goes to amplifier #3. This is also an IC instrumentation amplifier (Analog Devices AD522A). Since the output of amplifier #3 is proportional to the difference between its input signals, it is necessary to reverse the inputs to amplifier #2 in order to get the sum of the terms. The output of amplifier #3 then gives a voltage proportional to V_x in equation 4.

The gain of amplifier #1 or amplifier #2 is determined by a potentiometer R_g connected between two terminals of the amplifier (not shown in Figure 1). The gain equation for the Burr-Brown 3629 amplifier is:

$$G = 5 + \frac{20000}{R_g} \quad (5)$$

Thus for a gain of 600, R_g = 34 ohms and for a gain of 1200, R_g = 17 ohms.

The output voltage of the multiplier is $\frac{Ex\ Ey}{10}$ where Ex and Ey are the two inputs. Potentiometer R1 is adjusted to 10 cos θ, however, so that there is no net loss at the multiplier output.

Amplifier #3 is used at low gain, e.g. G = 10. The gain equation of the AD 522 amplifier is

$$G = 1 + \frac{2 \times 10^5}{R_g} \quad (6)$$

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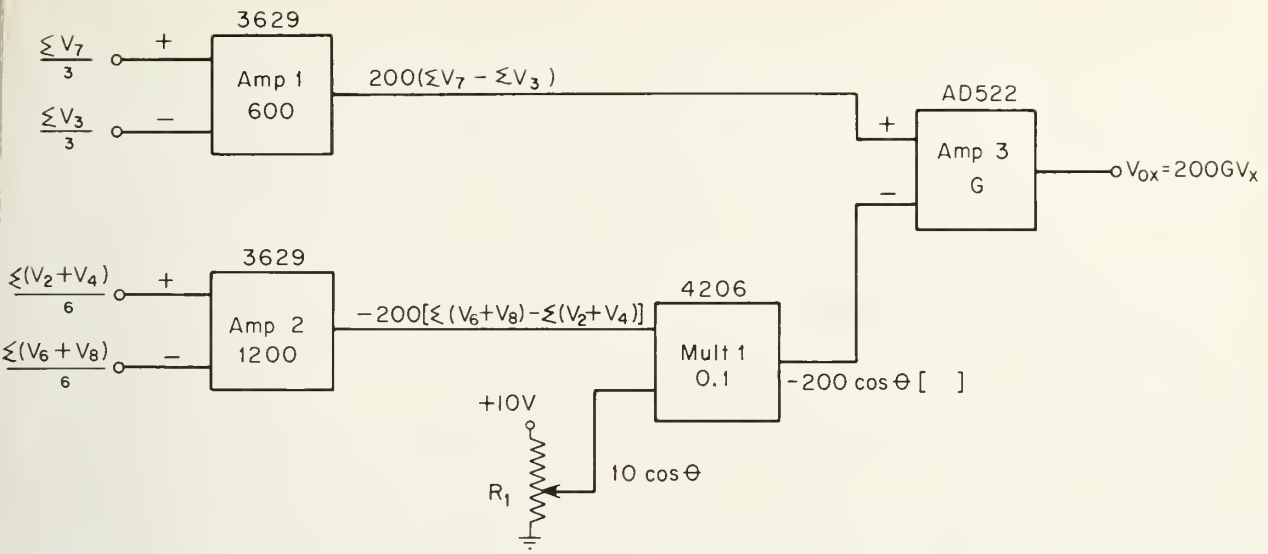


Figure 1. M_x circuit. The circuit for M_z is identical except that the potentiometer is set to 10 sin θ and different electrodes are used.

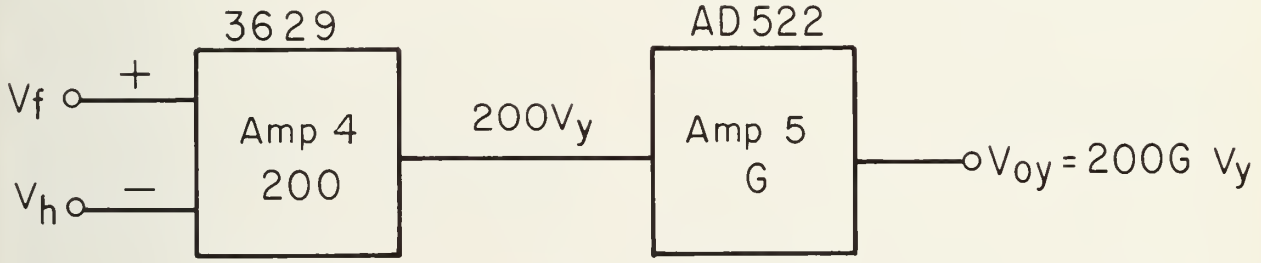


Figure 2. M_y circuit.

so that for a gain of 10, R_g = 22 K ohms.

The equation for M_z is:

$$M_z = \frac{k\,HP}{32}\left\{\Sigma(V_1 - V_5) + \sin\theta\left[\Sigma(V_2 + V_8) - \Sigma(V_4 + V_6)\right]\right\} \quad (7)$$

The circuit for M_z is identical to Figure 1 except that the multiplier potentiometer is set to 10 sin θ and different electrodes are connected to the inputs through 500K summing resistors.

Equation 2 is used for M_y. Amplifier #4 (Figure 2) is also a Burr-Brown 3629 with inputs connected to electrodes on the head or neck and to the left leg. The right leg is grounded as in common practice. The power supply for all IC units is ± 15V DC so that there is little danger of electrical shock. For extra precaution, however, 500K resistors can also be used at the inputs of amplifier #4. Since the input impedance of the 3629 amplifier is 10^{10} ohms, the 500K input resistors result in negligible loss of input voltage, although the noise level increases somewhat.

The output voltages from the networks are then:

$$\begin{aligned} V_{ox} &= 200\,G\,V_x \\ V_{oy} &= 200\,G\,V_y \\ V_{oz} &= 200\,G\,V_z \end{aligned} \quad (8)$$

where G is the gain of the output amplifiers. These voltages must be multiplied by thorax dimensions in order to get accurate results. Since

$$\begin{aligned} M_x &= \frac{k\,HP}{32}\,V_x \\ M_y &= k\,S\,V_y \\ M_z &= \frac{k\,HP}{32}\,V_z \end{aligned} \quad (9)$$

we have

$$\begin{aligned} M_x &= \frac{k\,HP}{6400}\,\frac{V_{ox}}{G} \\ M_y &= \frac{k\,S}{200}\,\frac{V_{oy}}{G} \\ M_z &= \frac{k\,HP}{6400}\,\frac{V_{oz}}{G} \end{aligned} \quad (10)$$

If the voltages are expressed in mV and k in ohm^{-1} cm^{-1}, the units of M are mA-cm. As an example, for our human thorax model[1], HP = 4714 cm^2 and S = 616 cm^2. For G = 10, and if $V_{ox} = V_{oy} = V_{oz}$ = 1000 mV, then:

$$\begin{aligned} M_x &= 74\,k\ \text{mA-cm} = 0.16\ \text{mA-cm} \\ M_y &= 308\,k\ \text{mA-cm} = 0.67\ \text{mA-cm} \\ M_z &= 74\,k\ \text{mA-cm} = 0.16\ \text{mA-cm} \end{aligned}$$

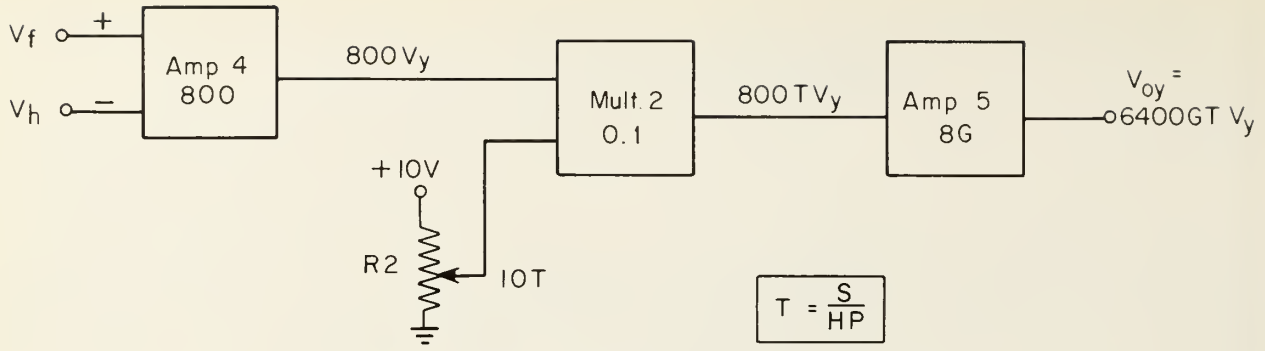


Figure 3. Alternative circuit for M_y used to obtain vector loops.

The values on the right were obtained using k = 1/463 ohm-cm for the human trunk[3].

Determination of cos θ and sin θ

In the equivalent ellipse used to represent the thorax cross section, θ is the angle between the normal to the body at electrode #8 and the +X axis[1]. The values of cos θ and sin θ at electrodes 2, 4 and 6 are the same or of opposite polarity due to symmetry. The value of θ depends only on the ratio b/a where b = semi-minor axis and a = semi-major axis. A table of θ as a function of b/a has been given previously[1]. In the appendix we give a table of cos θ and sin θ vs b/a for convenience. Equation 10 can be used for determining M_x, M_y and M_z. From these values, M, H° and V° can be calculated, where M = spatial magnitude, H° = horizontal angle and V° = vertical angle[1].

Production of Vector Loops

In order to measure vector loops directly by means of an oscilloscope or X-Y recorder, the three output voltages V_{ox}, V_{oy}, V_{oz} should have the same factors of proportionality to M_x, M_y and M_z, respectively.

Equation 10 can be rewritten:

$$V_{ox} = \frac{6400\,G}{k\,HP} M_x$$

$$V_{oy} = \frac{200\,G}{k\,S} M_y \qquad (10a)$$

$$V_{oz} = \frac{6400\,G}{k\,HP} M_z$$

The objective now is to express V_{oy} in the same form as the other two equations. Figure 3 shows a circuit for M_y which will accomplish this purpose. The potentiometer R_2 is set to the value of 10T, where T = S/HP. Amplifier #4 is set to a gain of 800 and the gain of amplifier #5 is made equal to eight times the gain of amplifier #3 in Figure 1. Then:

$$V_{oy} = 6400\,GT\,V_y = 6400\,G\frac{S}{HP}V_y$$

and since $V_y = \frac{M_y}{kS}$

$$V_{oy} = \frac{6400\,G}{k\,HP} M_y \qquad (11)$$

Equation 11 is then identical to the first and third equations of (10a).

Discussion

Although the circuit of Figure 3 appears to have much more gain than that of Figure 2, this is partly compensated for by the fact that T is usually a fairly small number. For our male and female human thorax models, T = 0.131 and 0.109, respectively. There will then be an attenuation of voltages through multiplier #2. The IC amplifiers will handle output voltages nearly equal to the supply voltage (± 15V). For large input voltages, it may be necessary to reduce the gains of the circuits of Figures 1 and 3 by equal amounts to prevent over-loading of the amplifiers.

The frequency response of the 3629 amplifier (amplifiers #1, 2 and 4) depends on the gain used. For a gain of 1000 the specifications state that frequency response is flat to 3.5 kHz within 3 db. Our own tests showed that with a gain of 1200, there was a 2.5% loss at a frequency of 1000 Hz and a 7% loss at a frequency of 1500 Hz. The phase shift was linear with frequency and was 22° at 1000 Hz and 33° at 1500 Hz. At lower frequencies there were smaller losses and phase shifts. The current price of the 3629 BM IC is $30.

The AD 522 (amplifiers #3 and 5) costs about the same but does not have as good a gain—bandwidth product as the 3629. At low gains, however, it is adequate. At gains up to 100, the frequency response is flat up to about 2000 Hz.

Another factor of importance in integrated circuits is offset voltage (output voltage with no signal applied). For the 3629, this is ± 25 ± 200/G μV, where G is the gain. The output voltage for a gain of 1200 would thus be 30 mV, but this is negligible in comparison with signal levels. The offset voltage of the AD 522 is higher but these amplifiers are used with low gain in this application.

The earlier multipliers required up to four poten-

tiometers for adjusting offset and linearity. The newer units are laser-trimmed and require no external potentiometers. The Burr-Brown 4206J, used in Figures 1 and 3, has a total error of 0.5%, an output offset voltage of 15 mV and a non-linearity less than 0.05% with no external trimmers. Since the input impedance of the multiplier used is 25000 ohms, R_1 and R_2 were chosen to be 1000 ohm potentiometers, taking a current of 10 mA each. The price of the 4206J is now $39. Total cost of all components, including the potentiometers should be under $500. The power supply should give ± 15V DC at 200 mA, and + 10V DC at 50 mA.

Rapid developments are taking place in the integrated circuit field and equivalent or better amplifiers and multipliers can be used instead of those specified. The 3629 IC can also be used for amplifiers #3 and 5 if desired. Similar circuits are being developed for the determination of dipole location[4].

Use of the Lead System

For human beings, the levels of the three rows of electrodes are determined by measuring the distance, H′, between the supra-sternal notch and the umbilicus[1]. Row B is midway between notch and umbilicus. Row A is located at a distance H′/8 above the umbilicus and row C at H′/8 below the notch. Then H, used in the equations, is given by

$$H = 1.5\,H' \qquad (12)$$

In some cases it may be better to use the anterior superior iliac spine as the lower landmark, since the umbilicus is somewhat variable in position. In any case, the locations of the electrodes are not critical and it is not necessary that any electrode be at the point of maximal potential on the chest wall. Eight electrodes are put on each level, at the midsternal line, center of back, right and left mid-axillary lines and midway between these points, as discussed above. The Y lead electrodes are connected to left-leg (+) and head or neck (−). The right leg is grounded.

The 500K summing resistors are located inside the metal box housing the circuits. Shielded cables from the box connect to the electrodes. The three output cables give vector voltages V_{ox}, V_{oy} and V_{oz}.

Hinged calipers are used to measure the left-right and anterior-posterior dimensions of the chest. Then a = one-half left-right distance and b = one-half anterior-posterior distance. The value of periphery P can be determined by a tape measure or can be calculated from:

$$P = 2\pi \sqrt{\frac{a^2 + b^2}{2}} \qquad (13)$$

The cross-sectional area, S, is given by:

$$S = \pi\, ab \qquad (14)$$

The values of $\cos\theta$ and $\sin\theta$ can be found from the table, using the measured value of b/a.

In case the arms intervene in the top row of electrodes, electrode #3 is put on the right arm and electrode #7 on the left arm. We measure b and a at the three levels and use average values, but for routine use it is sufficiently accurate to take a single measurement.

The procedure for animal vectorcardiograms is exactly the same except for the locations of the three rows of electrodes. In general, the "range of integration", H, is the distance between the two levels above and below which the electrocardiogram is either very small or remains constant around the thorax periphery. We assume the potential of the head is constant. The lower level must be determined experimentally for each species. For the dog and pig we used the distance between the humerus and a point midway between the xiphoid and the ilium[5,6]. For the monkey, H is the distance between the base of the jaw and the anterior spine[7]. The lead system has also been used on the rabbit and the rat[8,9]. In the rabbit the lower level was found to be at the caudal border of the rib cage[8]. With animals the distance, H, is simply divided by four to locate the electrode levels.

Summary

An inexpensive vectorcardiograph using integrated circuits is described. The size of the instrument can be made to be very small. Output voltages are directly proportional to the X, Y and Z components of the heart dipole moment, M. The inclusion of thorax dimensions in the determination of vector magnitude provides greater accuracy than currently used vector lead systems[10]. The system can be used with animals as well as young children and adults with no loss of accuracy.

Appendix

$\cos\theta$ and $\sin\theta$ as a function of b/a

b/a	$\cos\theta$	$\sin\theta$	b/a	$\cos\theta$	$\sin\theta$
.20	.136	.991	1.05	.734	.679
.25	.170	.985	1.10	.755	.656
.30	.204	.979	1.15	.775	.632
.35	.243	.970	1.20	.793	.609
.40	.281	.960	1.25	.812	.584
.45	.321	.947	1.30	.827	.562
.50	.358	.934	1.35	.842	.540
.55	.396	.918	1.40	.852	.524
.60	.435	.900	1.45	.863	.505
.65	.471	.882	1.50	.873	.488
.70	.512	.859	1.55	.880	.475
.75	.547	.837	1.60	.890	.456
.80	.584	.812	1.65	.899	.438
.85	.613	.790	1.70	.908	.419
.90	.649	.760	1.75	.912	.411
.95	.678	.736	1.80	.916	.402
1.00	.707	.707			

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Hypernatremic Dehydration in Infancy as a Presenting Sign of Underlying Disease

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ABSTRACT

We report two infants with underlying disease who presented with hypernatremic dehydration as the initial manifestation of their illness. Both had mild intercurrent infections with fever, but neither had significant gastrointestinal losses or intake of inappropriately high solute feedings to explain their hyperosmolar dehydration. Increased insensible losses from fever and tachypnea, poor oral intake and inability to concentrate the urine resulted in hypernatremia. This case report emphasizes that infants who present with hypernatremic dehydration in the absence of appropriate symptomatology should be evaluated for underlying renal or CNS disease.

INTRODUCTION

Hypernatremic dehydration is commonly encountered in children less than a year of age. Ten to twenty percent of infants in that age group hositalized for dehydration will have serum sodium values above 150 mEg/L.[1] Hypernatremia in these cases is thought to result from acute gastrointestinal losses and/or from formulae with inappropriately high solute loads. Much less commonly encountered is hypernatremic dehydration in the absence of obvious predisposing causes. We report two children presenting with acute hypernatremic dehydration and only mild gastrointestinal losses, both of whom were subsequently found to have biochemical renal defects and inability to concentrate urine. This paper's purpose is to emphasize the need to be suspicious of underlying pathology when hypernatremic dehydration occurs in the absence of appropriate symptomatology.

CASE REPORTS

Case 1. H.I. was born at term to a Gravida 2, Para 2, 25-year-old mother whose pregnancy and delivery were uncomplicated. Birth weight was 3.1 kilograms, and the neonatal period was uneventful. When seen by her pediatrician at six weeks, she was failing to thrive. There were no physical abnormalities and the infant reportedly fed well. The mother was given specific feeding instructions and weight was checked frequently, without improvement in growth. Two days prior to admission, at three months of age, she became increasingly fussy, had infrequent firm stools, and was less interested in feeding. The night prior to admission the child was breathing heavily. The next day she was found to have low grade fever, hyperpnea, and dehydration. In the preceding twenty-four hours she had vomited once and had had no stools. She was being fed a ready-to-feed formula.

On admission, the infant was alert but fussy and emaciated. Height and weight were below the 3rd percentile and dehydration was estimated to be five percent. Vital signs included: temperature 37.6 (C), pulse 168, and respirations 80. Admission serum studies included a BUN of 48 mg%, NA 163 mEg/L, Cl 157 mEg/L, and HCO_3—◄10 mEg/L. Arterial blood gases were p02 63, pC02 22, pH 6.98. Urinalysis showed a specific gravity of 1.008, pH 7 and no glucose, protein, cells or casts. There were no renal calcifications on the KUB.

The child was rehydrated intravenously over 72 hours with solutions containing $NaHCO_3$. The urine pH was 6 on one subsequent occasion while acidosis was still present but otherwise always recorded at 7. The diagnosis of distal renal tubular acidosis was confirmed, and the patient was begun on a modified Shohl's solution. Weight gain began immediately in the hospital, and since that time she has been thriving and developing normally on a regular diet and periodically adjusted doses of Shohl's solution.

Case 2. B.T. was a white male born at term to a 23-year-old Gravida 1, Para 1 mother whose pregnancy and delivery were normal. The child did well in the first months of life, but between the third and sixth months his pediatrician noted a fall in his weight from the 25th to the 3rd percentile. He had no illnesses or episodes of dehydration, and he appeared to feed eaglerly. For the first 6 months he was nursed, did not crave liquids, and was described as a happy, placid child. Growth continued along the 3rd percentile. During the eighth month, he was weaned to low-fat, protein fortified milk supplemented with a variety of table foods.

One day prior to admission at 9 months of age, he developed a high fever. Bilateral otitis media was diagnosed and Ampicillin, acetaminophen and clear liquids were prescribed. During the night he vomited twice but continued to take clear liquids well. He had no diarrhea and urinated normally. The next day he was seen again with high fever, irritability and a bulging fontanelle.

On admission, he was small and well-proportioned, alert but irritable and appeared mildly dehydrated. Vital signs were: temperature 39 (C), pulse 140, and respirations 30. Weight was 7.3 kilograms. The fontanelle was full, and he had red, bulging tympanic membranes. Admitting serum studies included a BUN of 46 mg%, Na-155 mEg/L, K-4.3 mEg L, Cl-119 mEg L and HCO-20 mEg/L. Urinalysis showed a specific gravity of 1.014, pH 5.5, with no glucose, protein, cells or casts. Lumbar puncture produced clear, colorless fluid under normal pressure. There were 3 red blood cells/cu mm, normal glucose and protein, and there was no growth after culture.

The child was given clear liquids by mouth. Over the next few days, his serum sodium fluctuated between 152 and 163 mEg/L, and the BUN fell to 12 mg%. Intake averaged 2000 ml per day, and the diagnosis of diabetes insipidus was considered. An intravenous pyelogram was normal. During water deprivation he lost 5% of his body weight, while serum osmolality increased from 282 mOsm/L to 297 mOsm/L and urine osmolality went from 124 mOsm/L to 204 mOsm/L. In the well-hydrated state his urine arginine vasopression concentration was 155 femtomoles/min; in the dehydrated state it was 159 femtomoles/min. (Values for normally hydrated adults are 50-60 femtomoles/min).* The high urinary vasopression concentration and dilute urine in the presence of dehydration confirmed the diagnosis of nephrogenic diabetes insipidus. He is currently doing well on a regimen of low solute formula together with an intake of 2500 ml per day.

DISCUSSION

Hypernatremia, as defined by a serum sodium greater than 150 mEg/L, is associated with many diseases. It is a common finding in normal infants dehydrated from gastrointestinal disease where water

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*Study performed at ILS Laboratories LTD., London, England.

loss occurs in excess of electrolyte loss. Excess solute intake, as in boiled skim milk or in feedings of inappropriately mixed formula, powdered milk or salt and water solutions can aggravate or produce hyperosmolarity. Patients in coma can become hyperosmolar as a result of highly concentrated feedings and limited access to free water.[2] Hypernatremic dehydration without those stresses suggests impairment of renal concentrating ability or deranged central control of serum osmolality. In CNS disease which affects the thirst and osmoregulatory centers, hypernatremia exists in the absence of dehydration, and water loading will not correct the hyperosmolar state.[3]

Premature infants are susceptible to hypernatremic dehydration in the absence of gastrointestinal disease, particularly when nursed under radiant warmers, phototherapy lights, or in nonhumidified isolettes, due to limited urinary concentrating capacity together with relatively large insensible losses from skin.[4] Full term infants are much more resistant to these factors because of less insensible loss through skin and better urinary concentrating ability.

Children with renal diseases in which concentrating power is deficient normally compensate by increasing water intake. When ill, they may be unable to consume enough water to maintain hemeostasis, and hypernatremic dehydration occurs in the absence of excessive gastrointestinal losses.[5] Similarly, a child who does not secrete antidiuretic hormone or whose kidneys are unresponsive to it is at great risk for becoming hypernatremic during illness.[6]

The present cases illustrate several points. Both patients failed to thrive for unknown reasons, and they both became dehydrated during an acute illness which led to poor intake and extra insensible losses from fever and rapid respirations. Both infants had renal lesions associated with limited concentrating ability, and inadequate water intake led to hypernatremic dehydration. Patients with renal tubular acidosis are known to have polyuria and concentrating defects, the cause of which is not clearly understood.[7] While not reported as a usual feature of distal renal tubular acidosis, the hypernatremic dehydration in the first case apparently resulted from a combination of poor fluid intake, diminished renal water conservation and increased insensible losses. It is interesting to speculate that the second infant may have been able to tolerate his nephrogenic diabetes insipidus in early life because of a low solute intake. He also was able partially to concentrate urine in the presence of moderately severe dehydration. Patients with limited concentrating ability, who are fed a diet high in protein and electrolytes, need extra water intake to maintain positive water balance. A trivial illness can tip the scale towards dehydration and hyperosmolality. Even normal healthy infants receiving high solute feedings have higher serum osmolalities when compared to breast-fed infants and may be more susceptible to hypernatremic dehydration during illness.[8]

Although few infants hospitalized for hypernatremic dehydration will have underlying pathology, a careful history and physical examination, as well as initial pertinent laboratory tests, should alert the physician to that possibility. Both infants presented here had grown poorly and neither had gastrointestinal losses which accounted for the degree of hypernatremia observed. Neither infant had been fed an inappropriately prepared formula. Both had relatively dilute urine for their degree of hyperosmolality and the infant with renal tubular acidosis could not acidify her urine, despite severe systemic acidosis. An evaluation of these factors in any infant presenting with hypernatremic dehydration should alert the physician to otherwise unsuspected CNS or renal disease.

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The Present and the Future for Cancer Testing by Alpha-Fetoprotein

A Review

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Introduction

Human alpha-fetoprotein (AFP) was the first embryonic and tumor-associated protein to be accepted as a valuable indicator in the diagnosis and the monitoring of cancer. In 1963, AFP was first independently discovered in chemically-induced mouse hepatomas by Abelev, et al[1] and in human hepatocellular carcinoma by Tatarinov.[2] Subsequently, AFP testing by immunodiffusion was suggested for laboratory diagnosis of hepatocellular liver carcinoma, because AFP was not ordinarily detectable either in cholangiocellular liver carcinoma or in secondary liver carcinomas and other nonmalignant liver diseases.[3-5] These observations were fully confirmed by several research groups.[6-12] Furthermore, AFP was found in the serum of some patients bearing malignant teratomas of the testis and the ovary.[6,9]

By radioimmunoassay, serum AFP levels could be measured in normal adult donors at a range of 1-40 ng/ml.[13,14] The elevated AFP levels within 30-500 ng/ml in normal individuals living in South Africa remain to be clarified.[15] As for the temporarily increasing AFP in patients with liver cirrhosis, it might be associated with high risk for the development of hepatocellular carcinoma.[16]

In early human embryogenesis, AFP is first synthesized by the yolk sac and later by the liver and apparently by embryonic gastrointestinal tract. AFP is the dominant serum protein between the 10th and 18th week of gestation when its concentration reaches 3-4 mg/ml, after which it slowly decreases so that at birth, levels are between 0,01-0,15 mg/ml (approximately 0,3-4% of the peak level in the fetus).[17-20] After birth, the serum AFP concentration falls rapidly during a few months to the normal adult level, i.e., less than 0,001% of the peak level.

This paper describes recent clinical observations concerning the use of the AFP test in malignant tumors of hepatic and nonhepatic origin.

Methods of AFP Determination

At present, several immunochemical methods for the detection and the quantitation of AFP in a variety of biological fluids are available (Table 1). The sensitivity and specificity of AFP determinations are critical to the evaluation of both clinical and experimental investigations. Several modifications of the immunodiffusion test reveal AFP sensitivity at the range of 1,000-5,000 ng/ml with an absolute specificity. Highly sensitive methods have also been developed for the measurement of AFP. First, the indirect immunoradioautographic method was used for the determination of serum AFP. This method appears to be about 15-30 times more sensitive than an ordinary gel precipitation, but keeps the absolute specificity of an immunochemical reaction. Second, the radioimmunoassay or enzymeimmunoassay also have been applied recently to AFP determination. The minimum detectable amounts of AFP are 0.1 and 1.0 ng/ml respectively.

Using these more specific AFP tests in a variety of tumors, new clinical applications of AFP have been defined, including the diagnosis and monitoring of germ cell carcinoma and some gastrointestinal tumors.

AFP in Cancer Testing

Primary Cancer of the Liver

In 1963, the presence of AFP in the serum of two patients was first associated with hepatocellular carcinoma by Tatarinov who subsequently suggested the immunodiffusion AFP test for differential diagnosis of primary cancer of the liver and secondary liver cancer.[2-5] Since AFP could not be found ordinarily in any pathological and cancerous conditions, including secondary liver cancer and cholangiocellular liver carcinoma, its finding in adult patients was considered[5] as the pathognomonic sign of hepatocellular carcinoma.

In 1967, the first confirmations of above mentioned clinical results were reported by three laboratories from Astrakhan,[7] Moscow[6] and Paris.[8] Table 2 summarizes results of the first five years of AFP clinical testing. More than 450 patients have been observed with a variety of tumors, including 110 patients suffering from primary cancer of the liver and approximately 500 patients having different nonmalignant diseases. Of 95 patients with a biopsy documented diagnosis of hepatocellular carcinoma, 78 patients had initial elevated AFP serum levels detectable by immunodiffusion, while control serum samples from normal adults and from patients with malignant and benign diseases were normally AFP-negative. Only one of the 481 nonmalignant cases with acute yellow atrophy had a detectable AFP level. Among the 347 cases of nonhepatic tumors, so-called "false-positives" were found in embryonal

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Table 1

The Sensitivity of Various Methods for Detection and Quantitation of AFP

Method	*Sensitivity in Ng/ml*	*Some commercial names and companies*	*Reference*
Single radial immunodiffusion in agar	2,500-5,000	Behringwerke, AFP plate (West Germany)	(21)
Double immunodiffusion with standard system	1,000-3,000	AFP test Gamaley Research Institute (USSR)	(22)
Counter-current immunoelectrophoresis	500-1,500	Hyland, AFP-test (Belg)	(23)
	800-1,000	AFP-Rapidophor (Austria)	
Hemagglutination test	50-500	FP test Machida (Japan)	(24)
Immunoradioautography	50-100	AFP-Radiotest (USSR)	(25)
Enzymeimmunoassay	1-10	Shino-test, Ltd. (Japan)	(26)
Double antibody radioimmunoassay	0-1-1	AFP kit Abbot (USA) CIS (Belgium)	(27)

Table 2

The First Steps of Cancer Testing by Immunodiffusion Test on AFP

Area and country	*Year and reference*	*Number of AFP positive samples in/out of*			
		Hepatocellular carcinomas	*Cholangiocellular carcinomas*	*Other than liver cancer*	*Non-cancer liver diseases*
Astrakhan, USSR	1963 (2)	2/2	0/1	0/8	0/38
Astrakhan, USSR	1964 (4)	3/3	0/2	0/13	1*/12
Astrakhan, USSR	1966 (5)	5/5	0/3	0/19	0/79
Moscow, USSR	1967 (6)	19/24	0/4	13**/226	0/68
Paris, France	1967 (8)	37/47	—	0/60	0/284
Astrakhan, USSR	1967 (7)	12/14	0/5	0/21	—
Total	5 years	78/95	0/15	13/347	1/481

*acute yellow liver atrophy after viral hepatitis
**testicular tumours

teratoblastomas of testis. Analogous results ranging between 42 and 87% were obtained in a variety of geographical areas (Table 3). Although there were differences in the percentage of AFP-positive hepatomas between Asia-African and Caucasian countries, application of AFP testing became absolutely necessary worldwide for the diagnosis of hepatocellular carcinoma. The specificity of AFP testing for hepatocellular carcinoma appears to be very high and not affected by racial, geographic or environmental factors. The geographical and ethnic differences of positive AFP tests in hepatocellular carcinoma could be explained by differences in age, sex, cancer size and the sensitivity of AFP detection.[39]

Immunodiffusion AFP testing was also used in a mass survey for primary cancer of the liver by two groups from Senegal and China (Table 4).

Immunofluorescent study has shown[40] that AFP is produced by only a part of tumor cells, and serum AFP levels can be correlated with the number of AFP-producing cells in the tumor. No correlation has been found with any of the clinical parameters investigated nor with the histological subtype or degree of differentiation of the liver cancer.[30]

Increased sensitivity of AFP measurement by different methods (Table 1) must be considered along with the specificity of such tests in the diagnosis of hepatocellular carcinoma. By indirect immunoradioautography an elevated AFP level could be found in serum of patients with infectious and serum hepatitis[43] as well as in Au-antigen-positive sera,[44] although the association Au-antigen and AFP had no close correlation. By radioimmunoassay, an increased percentage of positive AFP tests was observed both in primary cancer of the liver and non-cancer

Table 3

The Presence of AFP in Serum of Patients with Hepatocellular Carcinoma in Different Countries (Immunodiffusion Test on AFP)

Country	Number of patients examined	Rate of positive cases	Reference
Indonesia	100	87	(28)
Hong Kong	42	64	(29)
Singapore	29	72	(30)
Japan	227	78	(31)
South Africa	130	78	(32)
Senegal	44	80	(30)
Mozambique	37	68	(33)
Uganda	40	50	(10)
France	30	60	(35)
Greece	35	51	(35)
Spain	17	42	(38)
England	41	43	(34)
USA	56	70	(37)
USSR	112	77	(36)

Table 4

AFP Test in Screening for Hepatocellular Carcinoma

Parameter	Senegal (41)	China (42)
Number screened	9,864	343,999
Total number elevated AFP	6	147
Number elevated AFP/100,000	60	43
Number apparent false-positives	0	18
Number false-negatives/total evaluable	3/9,864	7/11,004
Number + AFP before clinical evidence/total evaluable primary liver cancer patients	3/9	33/53

liver diseases as well as in other noncancer diseases (Table 5). In spite of this decrease in the specificity of the AFP radioimmunoassay quantitative determination of AFP by radioimmunoassay is valuable for the monitoring of effective treatment of hepatocellular carcinoma by surgical resection and/or chemotherapy[45]. It is important that in such cases the increased AFP level indicates residual liver cancer cells either at the primary tumor site or in metastatic organs.

Thus, less sensitive AFP tests are more important for the immunodiagnosis and the screening of hepatocellular carcinoma. At the same time, more sensitive AFP tests are valuable for the monitoring of AFP-producing tumors.

Germ Cell Tumors

The relationship between AFP and so-called embryonal teratocarcinomas of the testis was first found by Abelev, et al[6] and Masopust, et al.[11] These results are listed in Table 5. Subsequently, these observations were confirmed and extended by many authors.[46-53] It has been shown that elevated AFP concentrations are always associated with endodermal sinus tumors both in gonadal and extra-gonadal sites.

Table 5

AFP in Blood Sera of Patients with Testicular Tumour[6]

Histological diagnosis	Number of patients examined	Number of positive reactions
Teratoblastoma with features of embryonal carcinoma	17	7
Teratoblastoma with features of seminoma and chorioepithelioma	8	1
Teratoblastoma	4	2
Seminoma	12	0
Chorioepithelioma	4	0
Tumour of the stroma cells	2	0
Total	47	10

Table 6

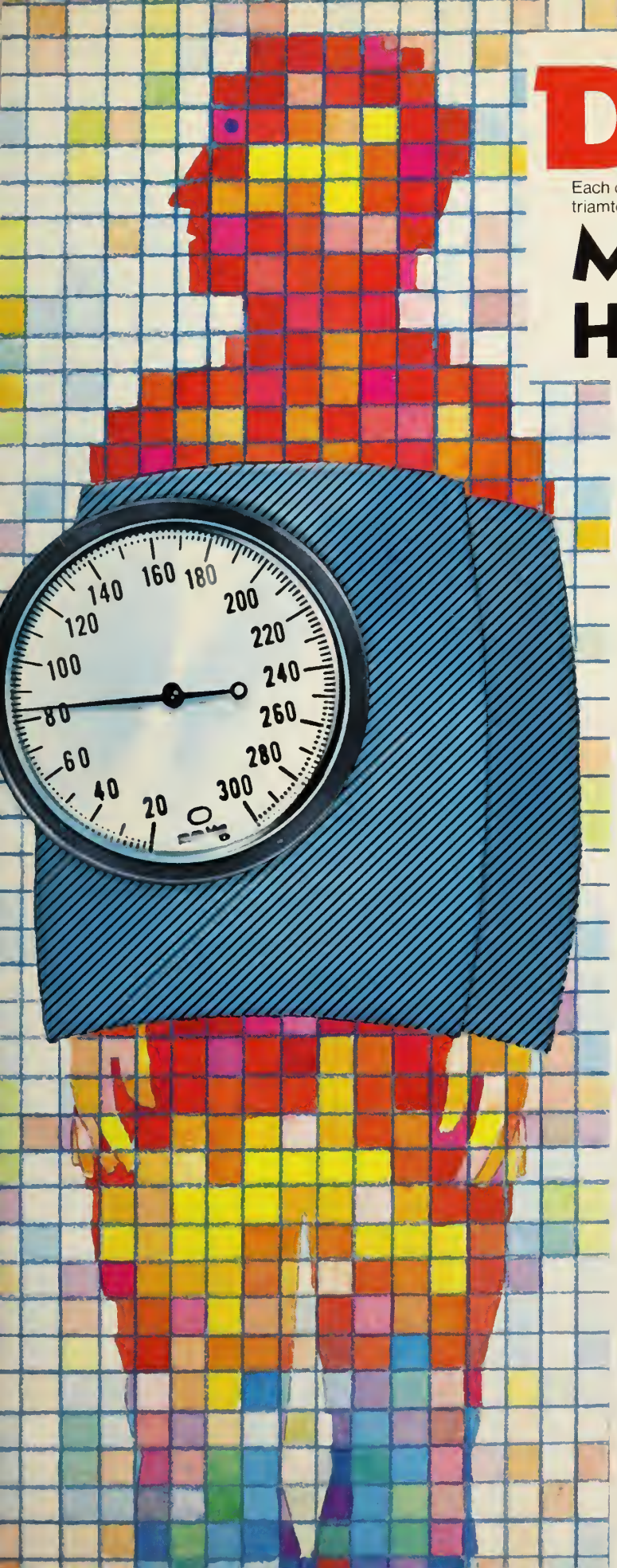
Occurrence of Elevated AFP Levels in Patients with Gastrointestinal Tumour[14]

Primary tumour site	Number of patients examined	Number positive reactions in percentage	
		immunodiffusion	immunoradioassay
Stomach	95	2	15
Biliary tract	8	0	25
Pancreas	45	2	24
Esophagus	4	0	0
Small bowel	10	0	0
Colon-rectum	191	0.5	3
Total	353	0.8	11.2

In accordance with the histological classification suggested by Teilum,[54] the differentiated forms of embryonal carcinoma may be separated into the following three types: 1) endodermal sinus carcinoma or yolk sac tumor, 2) choriocarcinoma, and 3) teratoma. In embryonal carcinomas, probably, there are a variety of combinations of these three types, including embryologically undifferentiated embryonal tumors. However, the cellular basis of AFP synthesis in embryonal carcinomas is epithelium of the yolk sac endoderm with the endodermal sinus origin.[50] This vitelline component which is producing AFP has similar origin with AFP-producing cells from fetal yolk sac or endodermal sinus in early embryogenesis.[55,56]

Since all embryonal carcinomas having endodermal sinus elements are associated with an initial increased serum AFP level, the measurement of AFP may be used for clinical diagnosis and for the estimation of prognosis. In addition, the AFP level may also be useful in the monitoring of surgical, chemotherapeutic and radiotherapeutic treatments of germ cell tumors.

Continued on Page 34



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†See Warnings, Precautions and Adverse Reactions.

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Reference:
King, J.C. and Starkman, N M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964

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Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS. Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: autonomic neuropathy; hepatic or renal disease; ulcerative colitis—Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon; hyperthyroidism; coronary heart disease; congestive heart failure; cardiac arrhythmias; and hypertension; hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.
It should be noted that the use of anticholinergic/antispasmodic drugs in the treatment of gastric ulcer may produce a delay in gastric emptying time and may complicate such therapy (antral stasis). Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia, urinary hesitancy and retention; blurred vision and tachycardia; palpitations; mydriasis; cycloplegia; increased ocular tension; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea, vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs.
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Product Information as of October, 1976

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TABLE 7

CANCER TEST VOLUME (THOUSANDS) FOR DIFFERENT AREAS IN 1976[60]

Test	*USA*	*Europe*	*Other*	*Total*
Acid phosphatase	3,000	2,000	1,000	6,000
CEA	1,300	80	50	1,430
AFP	50	75	250	375
human chorionic gonadotropin	200	50	25	275
Calcitonin	20	10	5	35
Total	4,750	2,215	1,325	8,115

Gastrointestinal Tumors

The first findings of AFP in serum of patients with other than hepatocellular carcinoma or embryonal teratomas were considered as so-called false-positive reactions.[30,36] However, further investigations[57-59] showed that several tumors having nonhepatic or nonendodermal sinus origins were associated with elevated serum AFP levels. Most often the elevated AFP levels were found in the patients with gastric, pancreatic and biliary tract tumors (Table 6). It is very important that AFP could be detectable not only by a radioimmunoassay but also by immunodiffusion in 2-3% of tumor cases.[14,58]

Comparative immunodiffusion studies have shown that AFP from patients with gastric and pancreatic as well as with colon carcinomas is identical to AFP from fetal serum and from the serum of patients with hepatocellular or embryonal cell tumors.[14]

It could be postulated that tumor cells from these AFP producing malignancies themselves possess the possibility of AFP synthesis. Apparently, AFP is a product of an activated embryonic gene which is suppressed in differentiated adult tissues. However, the origin and mechanism of AFP synthesis in nonhepatic and nonembryonal cell tumors remains to be studied.

Although the AFP test is not applicable for the early diagnosis of gastrointestinal tract malignancies (excluding hepatocellular carcinoma), serial quantitation of AFP in proven AFP producing tumors may be used for the indication of cancer activity and for evaluating the effectiveness of surgery and/or chemotherapy.

FUTURE OUTLOOK IN CANCER TESTING BY AFP

During the last 15 years, the AFP test has been extensively investigated both in primary cancer of the liver and in embryonal carcinomas as well as in other malignant and benign diseases. At present, the AFP test is employed worldwide both in cancer testing and in the testing of maternal and fetal disorders. For comparison, in 1976, the AFP test was more employed in Europe and in other areas (excluding the United States), while at the same time, acid phosphatase and CEA tests were more used in the United States than Europe or Asia (Table 7). According to King's hypothesis,

Table 8

Cancer Testing by Different Markers and Future Test Volume Worldwide[60]

Test	Year (in thousands)			
	1976	1977	1978	1980
Acid phosphatase	6,000	6,500	7,000	8,000
CEA	1,430	1,800	2,500	4,000
AFP	375	425	900	1,600
HCG	275	350	450	700
Calcitonin	35	40	50	100
Total	8,115	9,115	10,900	21,600

AFP should show the most dramatic growth by 1980, primarily because of the potential for fetal neural tube defects.[60] This supposition is shown in Table 8.

In the near future, AFP will be combined with a variety of immunochemical tests such as CEA, acid phosphatase, human chorionic gonadotropin and other placental proteins to discover new criteria for cancer activity and to help find a more correct approach to chemotherapy and immunotherapy of tumors.

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The Treatment of Sarcoidosis

Barry L. Fanburg, M.D.

Abstract

Sarcoidosis is a disease of unknown etiology characterized histologically by a granulomatous process with cellular infiltration. The granulomatous changes may remit spontaneously or may develop into fibrosis that, at times, is severe; factors that influence these progressions of the disease are not known. Cellular and humoral immunological abnormalities may be associated with this disease. Any organ can be affected although there is a high frequency of pulmonary involvement. Corticosteroids, the single most effective therapy, cause temporary remission of the granulomatous changes but do not influence established fibrosis. Likely, corticosteroids only temporarily influence the natural progression of sarcoidosis. However, corticosteroid therapy can preserve the function of vital organs. Other forms of treatment, such as chloroquine and methotrexate, also produce remissions of the granulomatous infiltrate of sarcoidosis but they offer no therapeutic advantages over corticosteroids. The decision of whether or not to treat is often a difficult one, since therapy has potentially hazardous side effects.

Introduction

The etiology of sarcoidosis is unknown, and its natural history in a given individual is unpredictable. Corticosteroids, the drugs most effective for treatment, have deleterious side effects and are not curative; when therapy is stopped, the disease may recur. Since physicians are frequently confronted with decisions on the treatment of sarcoidosis, a rational approach to therapy is necessary.

Evidence for the transmissibility of sarcoidosis has been sought but the disease appears not to be infectious.[1] The theory that inhaled or ingested agents might initiate the disease is unsupported. Nor is there evidence to support genetic determination of sarcoidosis.

Whatever the origin of the disease may be, alterations in the cellular immunological system eventually develop. This is characterized by a combination of both accentuation and repression of cellular and humoral immune responses (Figure 1). The histology of the sarcoidosis lesion typically consists of a granulomatous process with cellular infiltration, suggesting an active attraction of immunologically competent cells into the involved tissue. At the same time, patients also may have a depressed peripheral cellular immune response as manifested by decreased skin sensitivity to antigens such as purified protein derivative or fungal extracts. Similarly, cellular immunity may be impaired as reflected by a decrease in circulating T lymphocytes.[2] Antibody formation by B lymphocytes may be increased. Thus, there is discordancy in the cellular immune response in different areas of the body.

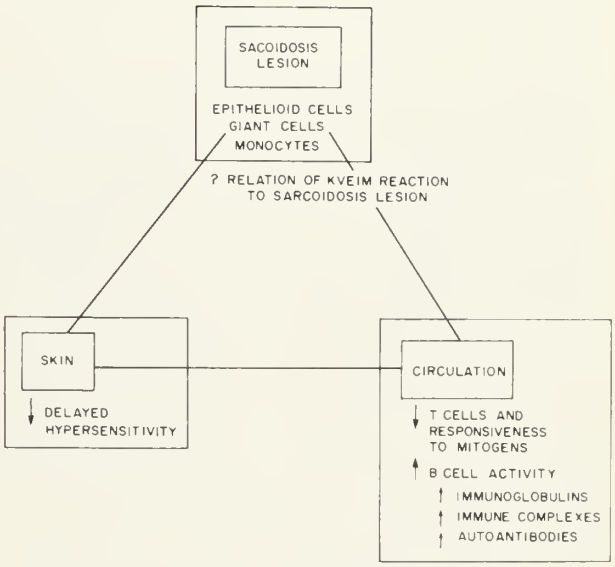


Fig. 1. Cellular and humoral immunological alterations in sarcoidosis.

Sarcoidosis may affect any organ of the body although there is a high frequency of pulmonary involvement. The granulomatous cellular response gradually evolves into fibrosis. The mechanism of this process is unknown, but it is possible that cells in the granuloma release substances (as in the case of macrophages)[3] that eventually may cause fibrosis, either by tissue destruction or by stimulation of connective tissue synthesis. Fibrosis develops slowly, sometimes over a period of years. The extent of fibrosis varies and may be severe; some fibrosis may be present even with the regression of the inflammatory response. Once formed, fibrosis does not regress. Hence, treatment is most important in the early stages of the disease, during cellular infiltration. Since cellular infiltration and fibrosis may coexist and involve the lung in a nonuniform fashion, random biopsy samples do not necessarily allow reliable evaluation of whole organ involvement.

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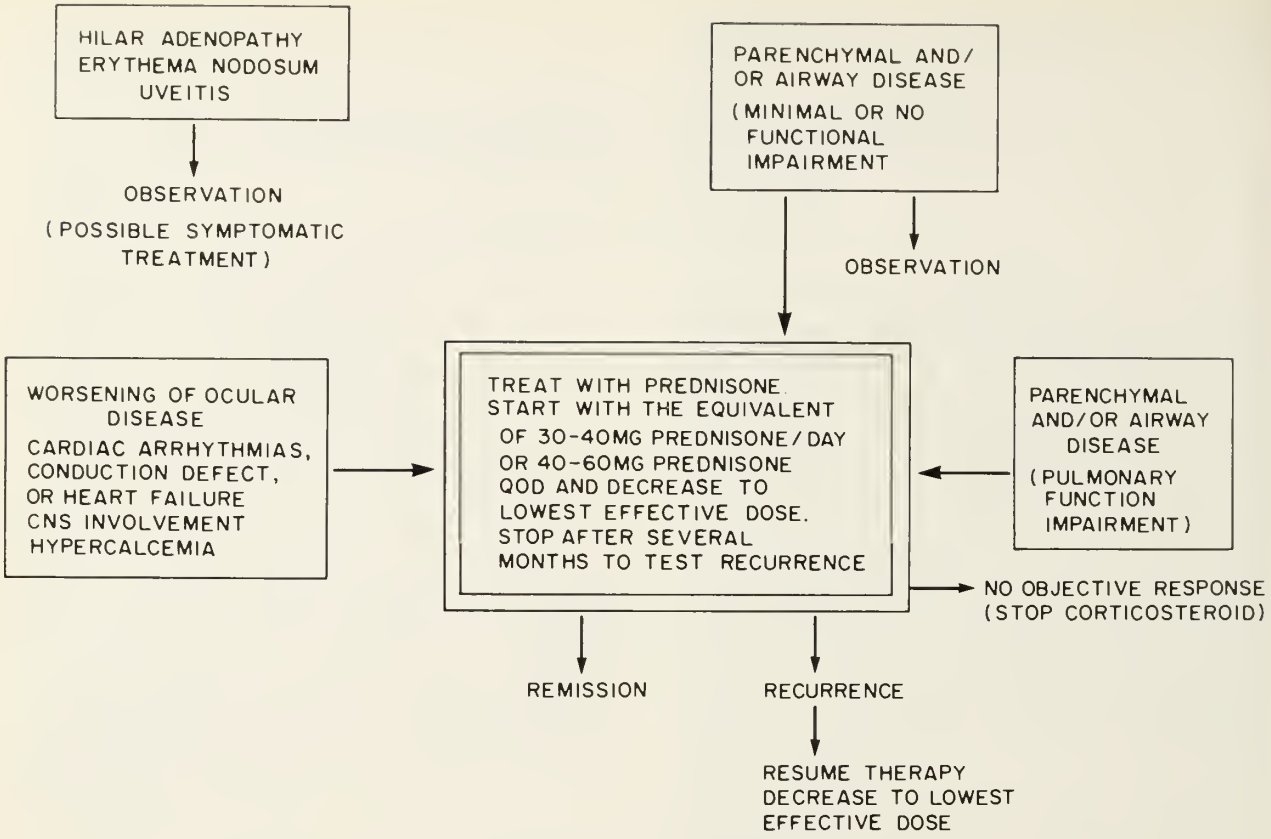


Fig. 2. Approaches to treatment of sarcoidosis.

Spontaneous Remission of Sarcoidosis

The possibility of spontaneous remission can complicate the approach to therapy of sarcoidosis. The spontaneous remission rate may be as high as 70 or 80%,[4] and is more common in those patients with overt disease limited to hilar lymphadenopathy with or without uveitis and erythema nodosum. In a controlled study of 37 patients with hilar lymphadenopathy, control and treated groups did not differ significantly either at the end of a three month period of treatment with steroids or at 5.2 years after completion of therapy.[5] Hence, in the relatively asymptomatic patient with these findings and normal pulmonary function, treatment generally is not needed (Figure 2). The patient with hilar lymphadenopathy and associated myalgia, more troublesome erythema nodosum, and fever (acute sarcoidosis or Loeffgren's Syndrome) may require anti-inflammatory agents such as aspirin or indomethacin; occasionally, corticosteroid therapy also may be used to control symptoms even though the overall course of the disease is not altered.[6] Remission may be associated with some degree of fibrosis, but this is not of concern as long as the function of vital organs is preserved. Once overt pulmonary parenchymal disease is evident, the incidence of spontaneous complete remission may decrease to approximately 30%.[7]

Decision Regarding Therapy

General Considerations

Although sarcoidosis may be benign and remit spontaneously, the overall case fatality rate can be as high as 10%[7-9] Corticosteroids are by far the most important of available treatments.[10] In a review of 15 years experience with 250 patients with symptomatic pulmonary parenchymal sarcoidosis treated with corticosteroids,[11] cellular inflammatory changes almost always responded, at least initially. A failure to respond is usually associated with significant fibrosis.

Steroid therapy has two major problems. First, the side effects are substantial, requiring careful weighing of potential benefits against possible complications. Second, there is no evidence that corticosteroids alter the eventual natural course of the disease process.[12] Hence, treatment with corticosteroids constitutes "buying time" for sarcoidosis to run its natural course with the minimal formation of fibrosis. It is conceivable that temporary remission with corticosteroid therapy could prolong the natural course of sarcoidosis. However, support for this hypothesis is lacking.[13]

No clear advantage has been demonstrated for any particular corticosteroid derivative. The most commonly used treatment is oral prednisone. A relatively low dose usually will produce a beneficial response. The usual starting dose is 30 to 40 mg prednisone or its equivalent per day.[11] Once a response is obtained, the dose is tapered to that which will maintain the response; this can be as low as 5 to 10 mg prednisone per day. Alternate day dosage may be as effective as daily dosage and may lead to a lower incidence of side effects.[14,15] Patients may respond very well to an

initial prednisone dose of 50 to 60 mg every other day, with subsequent tapering to the lowest level which will maintain remission,[16,17] or they may be started on daily steroids and changed to an every other day schedule once response is achieved. There has been some interest in using beclomethasone dipropionate, an aerosolized corticosteroid preparation, in the treatment of pulmonary sarcoidosis, since it has minimal systemic side effects.[18] However, this preparation has not been sufficiently tested to know if it is effective in sarcoidosis.

The high frequency of recurrence with discontinuation of steroid therapy[19] suggests that the natural course of the disease is altered only temporarily. Thus, therapy may have to be continued indefinitely.

Tuberculosis no longer is a common complication in patients treated with corticosteroids,[4] probably because of more accurate initial diagnosis. Routine antituberculous therapy in sarcoidosis patients receiving corticosteroids appears unnecessary unless tuberculin skin tests are positive.

Identification of Candidates for Corticosteroid Therapy

There is considerable variability in the threshold of physicians for the use of corticosteroids in sarcoidosis. This is evident from world-wide studies which show that the percentage of sarcoidosis patients treated with cortiocosteroids varies from 10 to 100%.[4] A committee of the Medical Section of the National Tuberculosis and Respiratory Disease Association in 1971 described the following indications for therapy of sarcoidosis:[12] (1) progressive pulmonary impairment or respiratory symptoms; (2) progressive impairment of visual acuity; (3) myocardial sarcoidosis with electrocardiographic evidence of conduction defects; (4) central nervous system sarcoidosis; (5) disfiguring cutaneous lesions; and (6) persistent hypercalcemia or hypercalcuria with renal insufficiency. They stated further that the majority of patients with subclinical or mild disease will have a spontaneous remission and need no therapy.

The most common type of sarcoidosis is represented by the asymptomatic patient with hilar lymphadenopathy with or without uveitis and erythema nodosum; this form of the disease was considered above. Steroid therapy is usually not indicated. The next most frequent patient group includes those with airway or parenchymal lung disease (Figure 2). For the patient with x-ray evidence of parenchymal lung disease but little or no respiratory symptomatology and normal pulmonary function, two approaches to treatment are possible: (1) the patient can be followed at two or three month intervals and treated if there is deterioration of pulmonary symptoms or function, or (2) the patient is treated with corticosteroids, responsiveness to therapy is determined, maintenance therapy is given for several months, then the drug is stopped. The patient may have a remission or the disease may recur when treatment is discontinued. Both approaches require long-term follow-up. There is no clear indication that one approach is better than the other for these types of patients.

Corticosteroid therapy is generally indicated for patients with significant pulmonary symptomatology or impaired pulmonary function (Figure 2) such as some combination of reduced lung volumes (restrictive disease), reduced diffusing capacity, or air flow limitation.[20] Impairment in pulmonary function usually is associated with radiologic abnormalities, but these may be minimal, particularly if the disease is located primarily around the airways or blood vessels. Corticosteroid therapy may not completely correct these abnormalities particularly when irreversible fibrosis is present.

Satisfactory clinical response occurred in a large percentage of 152 patients with symptomatic parenchymal sarcoidosis treated with steroids.[19] However, 78% of these patients relapsed when treatment was stopped. When treatment is successful, improvement usually occurs within several weeks. Little further improvement can be anticipated after that time. When there is no objective response to therapy within several weeks, the risk of long-term treatment outweighs the benefits and corticosteroids should be discontinued. Another trial of corticosteroids can be considered at a later date if an exacerbation develops.

Criteria for Assessing Responsiveness to Corticosteroid Therapy

Criteria for assessing possible improvement in pulmonary sarcoidosis fall into the categories of subjective, roentgenologic, and functional. Often the first indication of improvement is in symptomatology. The chest x-ray may show clearing while pulmonary functional impairment remains,[21-23] or x-ray abnormalities can remain despite improvement in pulmonary function. Hence, pulmonary function shows variable responses to corticosteroid therapy,[24] and it is difficult to predict which functional parameter will improve the most. Vital capacity often improves more than diffusing capacity.[11] A markedly decreased diffusing capacity may indicate a poor prognosis since it can indicate pulmonary vascular involvement and possible pulmonary hypertension. Endobronchial sarcoidosis may show improvement in flow parameters with therapy. Also, lung volumes may increase with therapy if there is atelectasis associated with endobronchial sarcoidosis.[25] The best general approach to assessment of effectiveness of therapy may be simply to follow all three parameters—chest x-ray, pulmonary function, and clinical symptomatology—in determining the amount and duration of therapy.

Extrapulmonary Disease and Response to Therapy

Almost any organ can be involved with the granulomatous and fibrotic changes of sarcoidosis. Spontaneous remission of granulomas may occur,

and disease in any organ may respond to corticosteroid therapy. Such varied involvement as cerebral granulomatosis,[26] myopathy resulting from granuloma,[27] and lacrimal sarcoidosis may respond to corticosteroid therapy.[5]

Impairment of any vital function is an indication for treatment. In particular, ocular, cardiac, and central nervous system involvement, or the presence of hypercalcemia should be treated[28-30] (Figure 2). In addition, there have been unusual cases of sarcoidosis of the kidneys with renal failure[31] and hepatic involvement with liver failure[32,33] which have responded very well to corticosteroid therapy. In optic and dermatologic sarcoidosis, topical and systemic corticosteroids may be combined advantageously to maximize therapeutic benefit with the least likelihood of side effects. The approach to corticosteroid therapy of extrapulmonary sarcoidosis is similar to that used for pulmonary disease.

Not all cases of extrapulmonary sarcoidosis will respond favorably to corticosteroid therapy. Cardiac arrhythmias, congestive heart failure, and cardiac conduction defects may not respond, perhaps due to the presence of fibrosis.[34] Myopathies resulting from sarcoidosis may show variable response.[35] Hypercalcemia generally responds well.

Other Drug Therapies of Sarcoidosis

A few medications other than corticosteroids, including chloroquine[36-40] and methotrexate,[41,42] are at least partly effective in the treatment of sarcoidosis. Oxyphenbutazone,[43] allopurinol,[44] and levamisole,[45] also have been proposed as treatments for sarcoidosis. Chloroquine and methotrexate may be more effective against cutaneous than against pulmonary sarcoidosis.[36,46]

There is no substantive evidence that the above medications may be more effective than corticosteroids, or might produce further improvement above that gained with corticosteroids. As with corticosteroids, these drugs are not curative. Because of the potential toxicity of chloroquine and methotrexate,[36,46,47] their use should be withheld unless corticosteroids are contraindicated.

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Tablets

PERCOCET-5 ®

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INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

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Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

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Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DDSAGE AND ADMINISTRATIDN Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

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Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The Maine Medical Association's House of Delegates, at its June 1976 meeting, adopted a regulation stating that a *minimum of 150* hours of continuing medical education is required in order to maintain membership. The policy took effect on January 1, 1977 and all members must be certified by January 1, 1980. Eligibility for certification begins January 1, 1977.

Credits required for the three-year period are as follows:

Category 1 — CME Activities with Accredited Sponsorship **(60 hours required)**	**No limit**
Category 2 — CME Activities with Non-accredited Sponsorship	**45 hours**
Category 3 — Medical Teaching	**45 hours**
Category 4 — Papers, Publications, Book and Exhibits	**40 hours**
Category 5 — Non-supervised individual CME Activities	**45 hours**
Category 6 — Other Meritorious Learning Experience	**45 hours**

Only active, dues-paying members are required to report. Please fill in your activity report promptly and return to the M.M.A. office, P. O. Box 250, Brunswick, Maine 04011.

SECOND SURGICAL OPINION

Beginning in January 1979, Blue Cross and Blue Shield of Maine will be conducting a pilot program in voluntary second surgical opinions for those members advised to undergo elective surgery. The program was designed in concert with the Maine Medical Association's Committee on Health Care Financing and it has the support of that committee.

When implemented, the program will enable an eligible member who has had surgery recommended and who desires a second opinion to obtain such an opinion from a surgeon, board certified in the surgical specialty appropriate to the recommended surgery.

In July of 1977, the participating Blue Shield surgeons were surveyed about participation in such a program, and over 75 percent of the respondents were in favor of participation.

The key elements of the program are:

1. The second surgical opinion benefit will be available to Blue Shield members who have had elective surgery recommended by his/her surgeon.
2. Procurement of a second opinion will be totally voluntary by allowing the member to decide if the second opinion will be obtained.
3. If the second opinion contradicts the initial recommendation for surgery and the member is in doubt as to the course of action that is best, a third opinion by another surgical specialist will be provided as a benefit.
4. The second opinion and/or third opinion from surgical specialists and the ancillary services necessary for such opinions will be provided without cost to the member. In addition, when the participating physician renders a first, second, or third opinion for a member's surgery, said physician shall agree to make fully available pertinent records, x-rays, test results, and other data to other physicians involved in the treatment of the member for the specific condition. Necessary tests not available to the specialist may be ordered at his/her discretion. The tests will also be provided without costs to the member.
5. Regardless of the outcome of the second and/or third opinion, covered surgical benefits are still available to the member if surgery is desired.
6. Consultants eligible to render second and third surgical opinions will be Board Certified (M.D.) surgeons or Certified Specialists (D.O.) in the appropriate surgical specialty.
7. The benefit to the surgical specialist will be the lower of his fee or $40 for the second or third surgical opinion. The specialist will agree to accept the benefit as payment in full. In addition, the specialist will agree not to perform surgery or otherwise treat the member for the specific condition involved, unless specifically asked by the member to do so, nor refer the member for treatment to any other physician with whom he or she is financially associated.

No physician shall be compelled to accept a covered member as a patient and nothing in the Plan's contract is intended to alter or change the normal relationship of physician and patient.

Letters to the Editor

To The Editor:

In a recent article in the Journal (Volume 69, Page 214, August 1978), Dr. George Davis raised the possibility that training mannequins used in teaching the psychomotor skills of cardiopulmonary resuscitation (CPR) may represent an important possible source of transmission of hepatitis and other diseases.

Despite widespread use (an estimated six to eight million Americans per year trained on the mannequins of one manufacturer alone), transmission of communicable diseases has not been reported or documented either in hospital personnel or in the general population. The possibility that CPR training mannequins act as fomites in the transmission of viral hepatitis B by contact with saliva positive for hepatitis B surface antigen (HBsAg) has recently been reviewed, and no cases of the disease have been reported as a result of use of these mannequins by persons known to have hepatitis B.[1,2] Furthermore, experimental protocols which have attempted to transmit hepatitis B by nasal or oral exposure of primates to saliva containing HBsAg have failed; in these studies the disease could only be transmitted after subcutaneous or intravenous injection of an infected saliva.[3,4] Two recent investigations of hepatitis B exposure, as reported in Morbidity and Mortality Weekly Report, suggest that transmission of hepatitis B to humans after oral contact with HBsAg-positive saliva is unlikely.[5] One of these exposures involved a group of hospital employees who participated in a CPR training program with a physician who became clinically ill with hepatitis B eight days after the training sessions. The patient's serum and saliva were positive for HBsAg by radioimmunoassay. None of the other class members became clinically ill and testing for the presence of HBsAg and antibody to the hepatitis B surface antigen over the subsequent six months was negative. Indeed, one of the participants in the training program, a nurse, was also the physician's wife. She did not develop clinical illness or positive laboratory studies during the six months after training. The mannequins had not been cleaned any differently from the technique described by Dr. Davis. During the practice of two rescuer CPR, the mannequin had not been cleaned between students so that at least half of the class had participated in two rescuer CPR training with the infected physician under these conditions. It seems unlikely, then, that CPR training mannequins act as fomites in the transmission of viral hepatitis B by contact with saliva positive for hepatitis B surface antigen. Furthermore, despite the potential for infection with other organisms, and despite the exposure of millions to this possibility, no significant infections have been reported. This, of course, does not obviate the possibility for such infection and for that reason guidelines for decontamination of cardiopulmonary resuscitation training mannequins have been developed and published by the Center for Disease Control.[6]

Therefore, unlike Typhoid Mary, with whom Dr. Davis compares CPR mannequins, these training instruments have not resulted in transmission of significant or reported illness. They have not "roamed the continent" without reason. Neither lectures, nor slides, nor movies have succeeded in adequately training health professionals in adequate performance of cardiopulmonary resuscitation.[7] Availability of the recording mannequin has been an important adjunct to teaching physicians, nurses, and ambulance personnel adequate technique in this critical skill. Finally, the justification for training of a wide segment of the general population in CPR is well founded. Cardiopulmonary resuscitation initiated by trained by-standers has been determined to be the most critical variable responsible not only for survival from prehospital cardiac arrest but also for the reduction of morbidity and neurologic dysfunction in such patients, even in those communities where rapidly responsive advanced life support units have been available.[8,9] Therefore, it is imperative that our professional efforts on behalf of these patients be complemented by timely application of CPR, as necessary, by the public. These skills cannot be taught without mannequin demonstration and practice. While we should certainly employ every possible measure to reduce the risk of infection to those we train, and maintain our surveillance for possible negative aspects of such training, we should not allow unfounded concern to obscure the need for this training and its impact on patient care.

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Costas T. Lambrew, M.D.
Educator, Emergency Medicine
Maine Medical Center and State of Maine EMS Project and Member, American Heart Association National Committee on CPR and Emergency Cardiac Care

Nancy Wynne, R.N., Chairperson
Basic Cardiac Life Support Committee
American Heart Association, Maine Affiliates, Inc.

H. Alan Hume, M.D.
Project Director
State of Maine Emergency Medical Services Project

Reply:

The tone of my original letter to the editor was designed to draw fire and stimulate thought about what we physicians do and advise. Apparently my goal has been achieved as the editorial by Dr. Lambrew demonstrates. His observations are accurate. As I alluded to in my addendum, there has been no absolute proof that Hepatitis B, for one, has been transmitted by these mannequins. Philosophically, however, it has always been true that no methodology or therapy is totally without risk, i.e., nothing seems to be all good (or indeed all bad). I only tried to point out that the modes of transmission or indeed the etiologies of many conditions are total enigmas. Not completely worked out is the mode of transmission of the EB virus (infectious mono or the "kissing disease"). Susceptibility at certain stages in life also plays an important role in the acquisition of certain diseases. The studies on the nature of "hepatitis C" are still in their formative stages. What causes Crohn's disease? Is Cave's virus real? Are lymphomas or leukemias virally mediated as many believe? My only point is that we should always be aware that no procedure is without risk. That society benefits from CPR training programs is obvious, but the risks which must weigh in the balance are beyond our knowledge at this time.

George E. Davis, M.D.
12 Spruce St.
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Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

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Incidence: Unmarked 1% to 3%; *3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

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County Society Notes

Hancock

The Hancock County Medical Society meeting was held on May 10, 1978 at the Hilltop House in Ellsworth.

Members present were Drs. Tyler, McIntyre, Bromley, Gurnee. Others present were the speaker, Jeanette Duym of the Hancock County Planning Commission and the members wives.

Mrs. Jeanette Duym, Committee Assistant, Hancock County Planning Commission told us the HCPC purpose is to: 1) provide cooperative efforts toward regional development, 2) prepare and maintain a comprehensive regional plan, 3) coordinate State and Federal planning and development programs, and 4) provide planning assistance and advisory services to municipalities. She gave us facts about the district and a history of the commission, starting with the 1968 formation of the Schoodic Peninsula Regional Planning Commission with members from the towns of Gouldsboro and Winter Harbor, Acadia National Park and the Winter Harbor Naval Security Group. Of the regions 35 towns, 32 towns are now members of the HCPC. The structure and methods of financing were explained. It was mentioned that 95% of the funds which go to Down East Health Services goes to administration. Mrs. Duym was thanked for her informative talk.

The minutes of the past meeting were not read. It was requested that members express disapproval of Sen. Hathaway's stand on Federal Certificate of Need. Hancock County wishes Mr. Hathaway to vote against extension of Certificate of Need in the future. Dr. McIntyre made the motion and Dr. Gurnee seconded it.

Dr. Morris Lambdin wrote from Samoa and wishes to retain membership in the Society. He falls in "affiliate" status—retired from active practice for the time being. Dr. Tyler will ask Dr. Winston Stewart to serve on the Committee on Health Care Financing.

Dr. Tyler also nominated Dr. John McIntyre for the Blue Shield award as well as the Hancock County Medical Society representative to the planning commission.

Because of the June 10th and 11th Maine Medical Association meeting, the Hancock County Medical Society meeting was to be on the first Wednesday of June, then decided to be the second Wednesday of September.

The Hancock County Medical Society meeting was held on October 11, 1978 at the Hilltop House in Ellsworth.

Members present were Drs. Tyler, Brownlow, Gurnee, McIntyre, Cravey, Dunham, Sucsy and Elkin. Guests were Dr. Lloyd Brown, Judy Sucsy, Sandra Phoenix and Dr. Lerner.

There was a cocktail hour from 6:30 to 7:30, followed by a dinner meeting. The Secretary's report was accepted with comment on the Down East Health Services by Dr. Sucsy. Treasurer's report was received and filed. There were no committee reports.

The Secretary summarized all correspondence he had received, with comments where applicable. Dr. Bradley Brownlow and Dr. Philip Elkin expressed willingness to participate in immunization programs. The Senator Hathaway vote in favor of including doctors under Federal Certificate of Need was again discussed. The memo concerning membership in the M.M.A. as being necessary for eligibility for Group Insurance plan, and disability insurance as offered by Morse, Payson and Noyes, as well as for membership in the County Medical Society and AMA was read by the Secretary and repeated. State, County and AMA dues were discussed. The need for CME was again emphasized, and a request made of the members to submit articles or news of interest for possible inclusion in the Journal of the M.M.A. The memo re nominations for vacancies on AMA council was read, as well as the notice of the Fall meeting of the M.M.A. House of Delegates in Waterville on December 9, 1978.

Dr. Lloyd Brown and Dr. Philip Elkin were introduced, as was incoming member Dr. Edward K. Dunham of Northeast Harbor.

Dr. Tyler circulated correspondence he had received; included one in which he was asked to comment on the agency involved in screening programs in our area; vacancy on AMA councils; and one from Dr. Hanley re Teaching Physician reimbursement.

Dr. McIntyre reported on his meeting with the Hancock County Planning Commission, defending his statement that "95% of the funds that go to the Down East Health Services goes to administration." Drs. Brownlow and Sucsy objected — the former saying he would submit facts and figures at the next meeting. Dr. Tyler will ask Dr. Randall Silver to be present and answer questions. Dr. McIntyre said he was impressed by the caliber of the members of the HCPC.

Drs. Brownlow and Gurnee had attended the June House of Delegates meeting in Rockport and submitted a report. A resolution was considered regarding the proposed M.M.A. building in Augusta, but it was felt best to have our delegates be guided by the facts presented December 9th in Waterville.

At the April 12th meeting, Dr. Howe of Blue Hill was elected the State Delegate with Dr. Fuller of Ellsworth as alternate. Neither wished to serve, and Dr. Brownlow went to Rockport on June 10 and 11, as well as Dr. Gurnee as Secretary. Dr. Tyler asked the membership for a vote for delegate and Dr. Winston Stewart was recommended.

A motion by Dr. McIntyre was made and seconded to "commend the well intentioned efforts of DECHS."

Dr. Tyler will try to obtain a representative of BC/BS for our December meeting. He requested the Secretary to have notices sent out two weeks prior to the meeting.

QUINBY D. GURNEE, M.D., *Secretary*

Washington

A regular meeting of the Washington County Medical Society was held on September 18, 1978 at the Peavey Memorial Library in Eastport, under the direction of Dr. James C. Bates, President of the Washington County Medical Society, with five members present.

I. Minutes of the last meeting, read and approved.

a) This was followed by a discussion of Down East Health Service, with an explanation of the various programs, by Dr. Donald M. Robertson of Harrington, Maine.

b) A motion was made, seconded and passed, that, for this meeting, we waive the usual waiting period for admission of new members.

c) The Society then moved, seconded and passed that Dr. Marshall I. Gladnick of Calais and Dr. John N. Bakke of East Machias be voted in as members of the Washington County Medical Society.

II. Dr. Christopher D. Mace was appointed Chairman of Diabetes Week.

III. Discussion of the Medical Mutual Insurance Company of Maine which is now in operation and is issuing policies as of September 1, 1978. Members are encouraged to join the Medical Mutual Insurance Company of Maine.

IV. Dr. Donald M. Robertson, Delegate of Washington County Medical Society to the Maine Medical Association, spoke about their proceedings at the last House of Delegates' meeting. He covered the various matters taken up. He also discussed the impossibility of our organization to negotiate with the Dept. of Human Services, or any third-party payers, to set up a uniform fee schedule.

a) It was suggested by him at the last House of Delegates meeting that we establish an Alternative Negotiating Committee which would be the only legal way to represent us with the Dept. of Human Services, or other third-party payers.

b) This will be brought up, in more detail, at the next meeting.

c) Dr. Robertson stated that we needed the interest of the younger members who will eventually have to carry on in our place. Efforts will be made to interest them, in the business and political part of Medicine.

V. Further discussion of the minutes of the last Executive meeting; discussion, also of the resolution on Cost Containment, with the members in favor of the resolution, as adopted by the Executive Committee, Sept. 9, 1978.

VI. The next meeting will be on Tuesday, October 17, 1978 at the Stable Inn, Calais, Maine. Dr. Francis Kittredge, President of

the Maine Medical Association, of Bangor, Maine, will speak on "Physicians Negotiating Agency." It is hoped that we can have a greater attendance from younger members, plus non-members and Osteopaths.

KARL V. LARSON, M.D., *Secretary*

Androscoggin

The Androscoggin County Medical Society meeting was held at Chase Hall, Bates College, September 21, 1978. The meeting was preceded by a social hour and dinner.

The meeting was called to order by the Vice-president, Dr. Lawrence A. Nadeau at 8:20 p.m., with 52 members and 13 guests present.

Dr. Nadeau presented two applications for membership, that of Drs. Robert J. Dalton and Paul R. Mailhot. Motion was made by Dr. Proulx, seconded by Dr. Fakhery to admit these doctors to membership. It was so voted.

Requests for change from active status to affiliate status from Drs. Dorothy Anderson and Paul J. Fortier were approved and voted unanimously.

Dr. Nadeau introduced the guest and prospective members to the Society: Drs. Robert Austin, Ayubi, Robert Dalton, Richard Fortier, Barry Kutzen, William Katz, Pierre Lachance, Lavine, Paul Mailhot, Philip O'Connor, Michael Rynne and David Walter.

The remainder of the business was postponed until after the speakers of the evening who were representatives of Blue Cross and Blue Shield were introduced by Dr. Nadeau. The panel included: Mr. Frank Faherty, Vice-president of Research and Provider Affairs, Mr. George Hansen, Vice-president of Finance, Mr. Max Powell, Vice-president of Marketing. Miss Elizabeth Walker representative of provider and professional relations was also present. They presented a most informative program on the History, Finances, Management and Processing of Claims. A lively question and answer period ensued.

At 10:20, Dr. Nadeau re-opened the business meeting. A motion was made by Dr. Thomas Shields and seconded by Dr. Grimes to adjourn. It was so voted.

The meeting adjourned at 10:25 p.m.

JULIETTE A. GIGUERE, R.N., *Assistant Secretary*

Kennebec

The Kennebec County Medical Association met at John Martin's Manor in Waterville on October 19, 1978. There were 48 members in attendance. A delicious Teriaki sirloin dinner was served in spite of the fact that the restaurant had not anticipated that many members to be there. There was no correspondence to be read.

Drs. Robert LaCava, John Sutherland, John van Summern, Brian Gardner and Eugene Peters were unanimously elected into membership. No new business was discussed.

Dr. Moore then introduced Mr. John Norton of the State Department of Human Services to discuss the State Planning Agency with the members of the Association. Mr. Norton gave a most lucid presentation of the organizational status of his Department and Bureau, and discussed with us several aspects of planning relative to the climate of today. Members seemed to receive this message very well and enjoyed the presentation.

O. THOMAS FEAGIN, M.D., *Secretary*

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Actinomycosis

David R. Ginder, M.D.*

Introduction

Since the introduction of antibiotics, the incidence, morbidity and mortality of actinomycosis has significantly decreased.[1,2] At least in part, this is so because Actinomycetes israelii and related organisms are inhibited/killed by a large number of commonly used antibiotics. However, with the declining incidence of disease, actinomycosis is not being considered sufficiently in the differential diagnosis. And in the laboratory where actinomycetes grow only anaerobically and frequently mixed with many other microorganisms, they can be difficult to grow and identify. Four patients with actinomycosis have been recognized at this hospital in the past five years and are the basis for the reminder that actinomycosis is still with us.

Clinical Reports

Table 1 relates the pertinent aspects of the patients. The first patient is described in detail to illustrate some common problems in establishing the diagnosis of actinomycosis.

A thirty-year-old housewife complained of peri-umbilical pain. Physical exam revealed a posterior pelvic mass. After appropriate studies, operation revealed a mass in the mid-transverse colon involving omentum and a similar mass deep in the pelvis. The preliminary pathologic interpretation was undifferentiated tumor versus inflammatory mass. No gram stains or cultures were reported. Thirty days later the pelvic mass was biopsied and revealed acute and chronic inflammation. Culture—no growth. No gram or special stains were done.

One month later the patient was re-admitted with right lower quadrant pain. Laparotomy revealed multiple pericolic abscesses about the colon mass and an abscess in the liver. The involved colon was resected. Multiple histologic sections revealed areas of necrosis, fibrosis and sulfur granules staining characteristically with Brown-Bren stain. Treatment consisted of large doses of parenteral penicillin followed by oral tetracycline. There have been no recurrences in the ensuing five years.

This patient illustrates the problem of differentiating actinomycosis from neoplasm early in the disease: the need to consider actinomycosis in inflammatory type lesion from which no organisms are cultivated; the importance of taking multiple sections and using modifications of gram stain to demonstrate sulfur granules in tissue; and the usual excellent response to appropriate antibiotic therapy.

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Microbiology

Actinomycosis is caused by A. israelii—a bacterium probably related to diptheroids. Two closely related gram positive nonspore forming anaerobic bacilli may also cause actinomycosis-like disease in man—Bifidobacterium eriksonii and Arachnia propionica. These organisms are either strictly anaerobic or microaerophilic. These are part of the normal flora of the body in gingiva, tonsils and gastrointestinal tract. Actinomycetes characteristically grow together with other anaerobic and microaerophilic bacteria to produce disease. The presence of the multiple anaerobes may cause difficulty in isolating and recognizing A. israelii.

Colonies of actinomycetes grow together to form sulfur granules that are white/yellow/brown and vary in size from 1-3 mm. Their recognition in exudate or histologic section is a helpful point in diagnosis. The characteristic appearance on gram stain is a blue central area surrounded by peripheral club like structures staining red. However, the granules are not always seen in actinomycosis and granules are not absolutely specific for actinomycosis.

Once separated the gram positive nonspore forming anaerobic bacilli are classified by various biochemical tests, particularly studies of metabolic products. Serologic tests are not sufficiently standardized or reliable for practical value.[3,4]

Pathogenesis

As in all infections that are caused by endogenous microorganisms, it is reasonable to assume that some break in host resistant allows the organism to cause infection. Thus, it has been observed that ac-

Table I

Patient	Site	S/S	Duration Before DX	Underlying Disease PPT Event	Diagnosis	Treatment After DX	Follow-up
30 yr. Housewife	Abdomen	Periumbilical Pain	2 mos.	None	B	Penicillin IV - 2 wks. followed by tetracycline PO - 6 mos.	5 yrs. No recurrence
17 yr. School boy	Neck	Mass Draining sinus	3 mos.	None	S C	Tetracycline PO - 3 mos.	3 yrs. No recurrence
34 yr. Secretary	Abdomen	Recurrent abscesses & sinuses	18 mos.	Diabetes mellitus	C	Tetracycline PO - 3 mos. to date	Currently receiving treatment
11 yr. School boy	Foot	Recurrent abscesses with draining sinus	3 mos.	Trauma to foot	C	To date Penicillin PO - 2 mos.	Currently receiving treatment

B — Biopsy with sulfur granules
C — Culture
S — Sulfur granules

tinomycetes cause: 1) mouth infections after tooth extractions, 2) lung abscess after aspiration, 3) gastrointestinal tract disease after appendectomy, and 4) gential tract infection after entry via IUD's.

Clinical Actinomycosis

Cervico-Facial

The initial stages of cervico-facial lesions may resemble other diseases that are associated with chronic inflammation. However, after a time when there is a purple-red indurated lesion with one or two sinuses, the possibility of actinomycosis should be evident.

Thoracic

Actinomycosis in the thorax most commonly begins as aspiration pneumonia. At this stage, it can only be distinguished from other causes of aspiration infection by isolating the organisms from a sample of sputum obtained from the bronchi.

In the past 10 years, it has been recognized that disseminated actinomycosis (an uncommon complication of actinomycosis) is particularly likely to occur in pulmonary actinomycosis.[5]

Gastrointestinal

Patient one of this report summarizes the problems of actinomycosis involving the gastrointestinal tract above the rectum and anus.

Primary ano-rectal actinomycosis presents the problem of recurrent abscesses and multiple fistulous tracts. At the Mayo Clinic between 1950-1972, 9 of 74 actinomycosis patients had primary ano-rectal actinomycosis.[6]

Gynecologic

In recent years, endometrial actinomycosis has been reported with increasing frequency. IUD's may serve as the route into the endometrium and beyond. The process resembles other chronic pelvic inflammatory disease and should be suspected when an IUD is present. The diagnosis can be sometimes made by examining the IUD.[7]

Pelvic actinomycosis associated with recto-sigmoid obstruction and dense pelvic and abdominal scarring can occur without evident disease by pelvic exam. In this situation, surgical investigation is hazardous and tissue samples frequently are inadequate to demonstrate sulfur granules and culture actinomycosis.[8]

Disseminated Actinomycosis

Metastases to skin, subcutaneous tissue and muscle is the hallmark of disseminated actinomycosis. The primary lesion is usually in the thorax where it may not be clinically evident. With treatment, prognosis is good.[4,9]

Diagnosis

The various clinical and microbiologic aspects of making a diagnosis are described below in terms of a clinical-pathologic approach:

1) When there are recurrent abscesses and draining sinuses suspect actinomycosis.

2) When repeated cultures in the situation described produce no growth, consider actinomycosis (as well as other anaerobic infections, fungal disease, tuberculosis etc.).

3) When exudate from lesions of the type described contain gram positive rods that do not grow upon aerobic cultivation think first of actinomycosis.

4) When exudate can be obtained from sinus tracts or from bandages, examine it with great care for sulfur granules. The technique is simple but it must be properly performed.[3,4]

5) When biopsy specimens from recurrent abscesses/sinus tract are examined, cut multiple sections to look for sulfur granules. Modifications of the gram stain (Brown-Bren) must be used to stain the sulfur granules in tissue.

Treatment

Actinomycetes israelii is sensitive to penicillin G, cephalosporins, erythromycin, lincomycin and clindamycin as well as tetracycline and chloramphenicol.

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Operant Pain
A New Name for an Old Problem

JOHN S. DIGGS, M.D.*

What is pain? What is chronic pain when there is no obvious cause? What do physicians do with a patient complaining with chronic pain when there is no evidence of a physical or organic cause?

This paper is written to discuss the problems created by our standard medical and surgical approach to chronic pain syndromes and to offer new ideas concerning the evaluation and treatment of chronic pain syndromes.

WHAT IS PAIN?

If you were asked by a lawyer in court in a case involving personal injury, "Doctor, please explain the meaning of pain," the only answer would be, "Pain is a symptom that a patient complains about." Unfortunately, this subjective complaint demands some form of objective understanding by physicians, the patient's family, the boss, the lawyer and judge, and the insurance company paying for the treatment and compensation. The social/economic pressures to apply a dollar value to a chronic complaint without objective findings when related to an injury leads to confusion, frustrations and false assumptions on the part of most people involved with the case.

The syndrome of chronic pain associated with disability is not restricted to litigation cases. The sequence of events that lead to the chronic complaint of pain can occur in the absence of compensation. For example, neck pain can persist with disability after settlement of an auto accident claim and, in reverse, not all pain of arthritis is disabling. Back pain with no money compensation can continue after one disc surgery and there are cases with persistent complaint of the same pain after five and six back surgeries. Complaint of pain will persist after a year of twice weekly spine manipulations. Why? What are we really dealing with? Because this syndrome is misunderstood, it is misdiagnosed and mistreated.

The lack of understanding of chronic pain leads doctors to overtreat the patient with surgery or pills. Lawyers oversimplify subjective complaints in their effort to come to some objective decision under the laws and in the process, the patient suffers an increased feeling of frustration and despair with unnecessary loss of time, money and often progression of pain with no relief of "sick behavior."

Ask any patient who has seen too many doctors for a chronic complaint if he was told or given the impression that his problem was all in his head. The answer will inevitably be "yes."

My interest in the question of chronic pain is a result of (1) The failure of the traditional medical/surgical approach in general and the clinical experience that pills/surgery and all the modalities of physical therapy cannot help some patients. Therefore, I am interested in looking for some other treatment program. (2) New knowledge of the techniques of behavioral sciences can explain both the causes and the appropriate treatment for chronic pain and its associated "sick behavior" which prevents a person from enjoying a normal life style.

THE PROBLEM "CHRONIC PAIN"

Once the internist, neurologist, orthopedist, neurosurgeon, phychiatrist and physiatrist (specialist in Physical Medicine and Rehabilitation) have ruled out the organic disease covered in their specialties, consideration must be given to the possibility that there is a behavioral component to the problem. Four points can be made:

1. *Pain is real.* "Psychogenic" and "psychophysiologic" are useless terms. It is a waste of time to question the complaint. Patients control their complaints. The only question is what can be done to treat the problem.
2. *Pain is influenced by learning.* Pain may start for any reason, but its continuation as a chronic problem comes under the control of learned behavior. A chronic problem is the result of a sequence of events through time. In my experience, back pain (non-organic) becomes *chronic* at three to six months.
3. *Learning or conditioning occurs all the time.* The circumstance of learning is a result of multiple factors not always controlled by the person suffering pain. The traditional approach perpetuates learning of sick behavior, but it is possible to prescribe a program to reverse learning toward well behavior.
4. After enough time has passed to establish chronic pain severe enough to prevent normal living patterns and all traditional methods have failed, there is a new approach to offer. *Abnormal behavior that has been learned can be reversed. The treatment must utilize behavior modification.*

Operant pain is the new term applied to the chronic pain due to unknown cause. Because of the behavioral and conditioning aspects of pain carried through time, the patient begins to operate from day to day with activity and pain behavior contingent on a predictable response from the people with whom he must deal. He exaggerates his complaints and physical findings in the doctor's office, because he expects a prescription for pain pills from the doctor.

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He develops a good history for the lawyer to establish an obvious connection between an injury and the complaint to satisfy the need for a cause of disability. A person with back pain cannot be examined by four and five physicians without learning what the back exam is all about and becoming conditioned to react to the next exam with increased evidence of dysfunction if there is any motivation to remain chronically ill. An experienced examiner in a severe case can detect the "hysterical response to back exam." The unwary or inexperienced will be fooled and diagnose back strain or lumbosacral arthritis and then order excessive treatment resulting in frustration, anger, and eventually failure for both the physician and the patient. The patient will conclude that he must be worse than most when all efforts are met with failure.

The problem is well stated by Dr. Patrick Wall in his opening paragraph of a chapter titled "Why Do We Not Understand Pain?" in a new book published in 1977 titled *"The Encyclopaedia of Ignorance."* Dr. Wall is a Professor of Anatomy at University College, London, and well known for his theory of gate-control of pain.

"Pain is. My pain, as it grows, is an imperative, an obsession, a compulsion, a dominating, engulfing reality. Your pain is a different matter. I observe you and listen to you. I sympathise with you by guessed analogy. If your state is beyond my ken, a woman in childbirth, a man passing a kidney stone, I am in particular difficulty. Even if I have experienced your particular situation, if I see you hit your thumb with a hammer, I not only remember my own pain but I recall my behavior and now I am in the dangerous situation of assessing the appropriateness of your behavior. Doctors and patients become extremely angry with each other when there is a mismatch between disease and the amount of pain which the doctor expects, especially if the patient has the impertinence to fail to respond to accepted therapy. At this point, the doctor begins to question if the pain is real or in the mind. What is this curious question asked by the observer but never by the person in pain?"[1]

From my clinical experience, the only mistake in the above paragraph is the fact that patients do ask whether their pain is in their mind. They come to this conclusion after seeing too many doctors and receiving the spoken or implied impression that their pain is not real and therefore must be in the mind. Some of these patients are improperly referred to a psychiatrist. Physicians who see a number of cases with no objective findings to account for pain will get rid of a patient by sending them to a psychiatrist, knowing they have no surgery or pills to offer. This is unfortunate because these patients are not "crazy." Because the physician does not know any other alternative evaluation and treatment, he will learn (conditioned behavior) the bad habit of shunting (getting rid of) the patient to a psychiatrist. This will tend to aggravate the problem, since this patient is not in need of a psychiatrist and the referral was inappropriate. The answer for "operant pain syndrome" is not psychiatric evaluation or treatment, but a referral to a specialized program under the direction of a psychologist with an interest in and knowledge of "chronic pain."

Evaluation of Chronic Pain

Evaluation of a patient that falls into the category of "operant pain syndrome" begins once the physician has a suspicion he is dealing with a case with no physical pathology, organic disease or neuromusculoskeletal damage. The first step in evaluation is, therefore, to objectively establish the absence of organic pathology. At this point the question can be raised, "If this patient is non-organic, could there be an operant syndrome?" No treatment can be offered without an operant evaluation.

Since the State of Maine does not have an established or specialized program for this problem, it is the purpose of this paper to suggest that all physicians become aware of the syndrome and develop some insight and a new idea of identification of this type of patient to at least prevent overtreatment medically and surgically, and inform the patient that there is no physical therapy, manipulative therapy, pills or surgery to offer, so that he might go to another state or medical center with such a program.

A physician can develop an impression of operant pain syndrome by identifying consistent patterns of chronic sick behavior. There must be a suspicion when the clinical findings do not support or account for the complaints. Further "red flags" are raised when the history shows

1. Underuse of medication: Usually means exaggeration of pain or a patient has no money to purchase expensive pills prescribed. Suggests a Workmen's Compensation case with high motivation to remain on Compensation checks and not use this money for any treatment or pills.
2. Overuse of pills: Usually seen in personality disorders with dependency features, inadequate personality, anxiety, depression, neuroses.
3. Long periods of daily, severe pain with no visits to a physician, emergency room or hospitalization and no tests or treatment: This type of patient goes to see the physician only when a lawyer or the insurance representative schedules an appointment. Even though the patient does not pay for visits in an insurance related pain problem, he demonstrates disinterest in seeking help. Since no one has ever shown much interest or help, he tends to give up in frustration with an undercurrent of anger against the system, making it more difficult for each successive health care service to deal with the problem.
4. Long periods of overtreatment: Usually physical therapy or manipulations with excessive hospitalizations or prolonged two or three times a week visits to the office of an osteopath or chiropractor for manipulations

including a variety of modality treatments. These generally give limited relief for one or two days, but no lasting improvement. Excessive, vigorous joint popping or snapping can cause progressive microdamage to facet joints of the spine while the stretching of the manipulation gives some degree of temporary muscle spasm relief. For this reason, patients develop a sense of false hope and continue treatment, although most will fall into the category of inadequate personality features as seen with overuse of any form of medication. If the patient overexaggerates (low pain threshold) the symptoms, the treatment is overutilized and will tend to produce side effects. Any form of overtreatment (pills, surgery, physical therapy) further convinces the patient there must be something physically wrong and that his case is an extra-complicated or difficult case justifying his continuing complaints.

5. Poor family situation: Separation, divorce, inadequate income for number of children to feed, and any other form of stress from socioeconomic difficulties. These problems should be referred for review and evaluation by a social worker.
6. Low education and poor job opportunities: When the patient knows he cannot do anything other than heavy labor and is not interested or motivated toward retraining, the outlook is bleak at best, adding to the motivation to remain in a compensated or welfare status.
7. Pre-injury personality abnormalities: This is a chicken and egg problem. Chronic illness usually leads to some anxiety and depression. A psychologist and his tests are required to try to establish whether the patient had a pre-injury personality which will usually include a triad, as measured on the MMPI (Minnesota Multiphasic Personality Inventory), consistent with the most severe types of operant pain syndrome, hypochondriasis, depression and anxiety. Add dependency and you have a patient who not only exaggerates symptoms, but easily becomes dependent on whatever might be offered in terms of surgery, pills or physical modalities.
8. Spouse: Oversupportive, undersupportive. The spouse might often be the individual demanding compensation if a patient happens to be an inadequate personality with dependency, depressive, anxiety features.
9. Anger toward: Job, job supervisor, doctors, lawyers, insurance companies and the entire rigamarole of the compensation process with endless appointments to the health care system, visits to lawyers, all leading to confusion, multiplication of questions with no answers.
10. The patient who demands an answer in face of normal laboratory, x-ray, and normal history and physical examination: These demands, plus anger, increase in relation to the number of physicians seen and tests done.
11. Too many physicians seen with conflicting opinions as reported to the next physician by the patient: This is usually misinterpretation of opinion by the patient.
12. Multiple surgical procedures with no improvement or only temporary improvement: The usual improvement after back surgery and operant pain syndrome is two weeks to two months, followed by return of same symptoms, usually a little worse than before surgery (placebo effect of surgery).
13. No interest in the cause of symptoms other than the fact it was caused by the injury. The patient states, "All this was from that accident because I never had trouble before."
14. No interest in a program of treatment and no interest in any home program requiring the patient to do something for himself. These patients demand that someone else (doctors, lawyers and therapists) tell them what is wrong and then proceed with treatment.
15. Heavy grime and callous formation of the hands: The patient who states that for two years he "cannot do anything" and presents to examination with evidence of manual labor on inspection of the hands, is not totally disabled.
16. Repeated statements: "All I want to do is go back to work, if only someone would make my back get better and take my pain away." (This means, "Someone else has to get me back to work because I cannot do anything for myself. I hurt too much all the time and my real doctor told me never to lift, bend, stoop, push or pull and signed a form stating I cannot ever work again.")
17. The same symptoms every day, 24 hours, with the quality of a "needle on a broken record."
18. Monthly compensation equal to or occasionally more than wages earned in a mill, factory, or in the woods, which is usually heavy, difficult, dirty, hot and "back-breaking" labor.
19. History of minor soft tissue bruising with symptoms lasting more than two to three weeks.
20. A patient who demands at the end of evaluation if the physician has found enough to prevent return to the job associated with injury: Direct questioning of the physician by the patient at the end of the interview can indicate the possibility of motivation to enter his two cent's worth into the decision-making process which the patient knows the physician and his lawyer must go through to get settlement at the next Workmen's Compensation hearing. Usually, the patient has been through this process long enough or is going to a second and third hearing, and he knows some of the ropes.
21. Retention of a lawyer in a patient with no

organic disease or findings consistent with history and complaint.

22. Side effects to medication or increased pain on a course of physical therapy.
23. Unused corsets, crutches and canes: Patients should be seen with their devices. These should be closely inspected for wear and usually will show only dust from time on the shelf. Patients will occasionally state that they use these devices "all the time."
24. Braces, collars and corsets that only make the pain worse.
25. Complaint of severe daily chronic pain in the summertime with a perfect and total body tan indicating time at the swimming pool or beach and usually found in a patient with a weekly compensation check.

Given the above "red flags" the physician is at the third step of what to do for this problem. To reemphasize: Step 1 is a specialty consultation with orthopedics, neurosurgery, neurology or physiatry to establish absence of organic disease. Step 2 is the suspicion of an operant pain syndrome. Step 3 is evaluation. This evaluation can only be done by a psychologist. Depending on the individual, evaluation might take one hour to as many as ten hours of testing, and consultation with both the patient and his spouse.

To try to convince my fellow physicians that "operant pain syndrome" is a syndrome and justifiable term, I offer the following two examples.

Conditioned behavior may lead to the chronic cough of a busy physician to gain the attention of a salesclerk in a store when he is in a hurry to buy a magazine, or on rounds when he desires the attention of his nurse or patient. It may also lead to the excessive demonstration of sick behavior by a patient that is learned after visiting too many doctor's offices for the purpose of seeking compensation for injury. The hysterical behavior in a chronic low-back patient can become so severe that the physician has difficulty sorting out the negative-positive aspects of an examination. Patients who have suffered chronic pain long enough cannot be examined in a 20 to 30 minute office visit. The doubt and frustration on the physician's part only helps to reinforce the opinion of the patient that "something must be physically wrong."

A more subtle example without the complication or motivation of compensation is illustrated in the book titled *Behavioral Methods for Chronic Pain and Illness* by Wilbert E. Fordyce, Ph.D., published by C. V. Mosby Company, St. Louis, 1976. Anyone interested or attempting to deal with patients demonstrating chronic pain and illness should have this book as required reading. This includes physicians, psychologists and physical therapists, and nurses who are part of an overall program.

"A housewife, perhaps while making a bed, experiences a sharp pain in her back, perhaps a muscle spasm. She straightens from her previously bent-over

Continued on Page 57

Tenuate ®
(diethylpropion hydrochloride NF)

Tenuate Dospan®
(diethylpropion hydrochloride NF) controlled-release

AVAILABLE ONLY ON PRESCRIPTION
Brief Summary
INDICATION: Tenuate and Tenuate Dospan are indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use such as those described below.
CONTRAINDICATIONS: Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors. (hypertensive crises may result).
WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. *Drug Dependence*. Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy*. Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children*. Tenuate is not recommended for use in children under 12 years of age.
PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.
ADVERSE REACTIONS: *Cardiovascular*. Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System*. Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal*. Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic*. Urticaria, rash, ecchymosis, erythema. *Endocrine*. Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System*. Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous*. A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.
DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride): One 25 mg. tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg. tablet daily, swallowed whole, in midmorning. Tenuate is not recommended for use in children under 12 years of age.
OVERDOSAGE: Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phentolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product Information as of April, 1976

MERRELL-NATIONAL LABORATORIES Inc.
Cayey, Puerto Rico 00633
Direct Medical Inquiries to
MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215, U.S.A.

Licensor of Merrell®

References: 1. Citations available on request—Medical Research Department, MERRELL RESEARCH CENTER, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M.T., O'Dillon, R.H., and Leyland, H.M.: A Comprehensive Review of Diethylpropion Hydrochloride. International Symposium on Central Mechanisms of Anorectic Drugs, Florence, Italy, Jan. 20-21, 1977.

Merrell

8-3921 (Y587A)

Whether overweight is a complicating factor... or just uncomplicated overweight.

Tenuate® Dospan® (IV)

(diethylpropion hydrochloride NF)

75 mg. controlled-release tablets



A useful short-term adjunct in an indicated weight loss program.

Overweight patients in certain diagnostic categories often require strict obesity control. Diethylpropion hydrochloride has been reported useful in obese patients with hypertension, symptomatic cardiovascular disease, or diabetes. While it is not suggested that Tenuate in any way reduces these complications in the overweight, it may have a useful place as a short-term adjunct in a prescribed dietary regimen. (Tenuate should not be administered to patients with severe hypertension; see additional Warnings and Precautions on the opposite page.)

In uncomplicated obesity.

Many patients, on the other hand, present with excess fat but no disease. While this condition is often termed uncomplicated obesity, complications of both a social and a psychologic nature may be distressingly real for the patients. In these cases, a short-term regimen of Tenuate can help reinforce your dietary counsel during the important early weeks of an indicated weight loss program.

Clinical effectiveness.

The anorexic effectiveness of diethylpropion hydrochloride is well documented. No less than 16 separate double-blind, placebo-controlled studies attest to its usefulness in daily practice.[1] And the unique chemistry of Tenuate provides "...anorexic potency with minimal overt central nervous system or cardiovascular stimulation."[2] Compared with the amphetamines, diethylpropion has minimal potential for abuse.

Tenuate—it makes sense. And it's responsible medicine.

Merrell

For prescribing information see opposite page











The evidence of experience

Since October 1974 when Motrin® (ibuprofen) was introduced in the United States, it has been used by more than 6,000,000 patients with rheumatoid arthritis* or osteoarthritis. Rarely has an ethical pharmaceutical product been prescribed for so many patients in so short a time. In addition, more than 450 studies presenting new data related to Motrin have been published.

The 6,000,000 patients already treated with Motrin is an objective measure of physicians' confidence in the ability of Motrin to relieve the pain and inflammation associated with rheumatoid arthritis and osteoarthritis.

So it is not surprising that in this short period Motrin has become the most frequently prescribed alternative to aspirin. Motrin relieves joint pain and inflammation as effectively as indomethacin or aspirin, but causes significantly fewer CNS and milder GI reactions. However, gastrointestinal bleeding, sometimes severe, has been associated with Motrin, aspirin, indomethacin, and other nonsteroidal antiarthritic agents.

*The safety and effectiveness of Motrin have not been established in patients with Functional Class IV rheumatoid arthritis (incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care).

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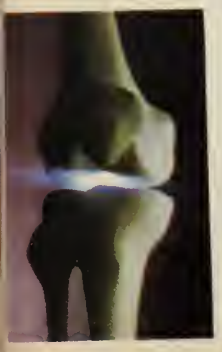












Motrin 400 mg TABLETS
ibuprofen, Upjohn

The confidence that comes from experience—
one more reason to prescribe Motrin.

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

I-6857

The confidence that comes from experience—
one more reason to prescribe

Motrin 400 mg TABLETS
ibuprofen, Upjohn

Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin* used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin (ibuprofen) is gastrointestinal (4% to 16%). This includes nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness*, headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

Incidence: Unmarked 1% to 3%; *3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Suggested dosage is 300 or 400 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day.

How Supplied

Motrin Tablets, 300 mg (white)	
Bottles of 60	NDC 0009-0733-01
Bottles of 500	NDC 0009-0733-02
Motrin Tablets, 400 mg (orange)	
Bottles of 60	NDC 0009-0750-01
Bottles of 500	NDC 0009-0750-02
Unit-dose package of 100	NDC 0009-0750-06
Unit of Use bottles of 120	NDC 0009-0750-26

Caution: Federal law prohibits dispensing without prescription.

NIM-3

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ALDOMET®
(METHYLDOPA | MSD)
TABLETS: 500 mg, 250 mg, and 125 mg

MSD
MERCK SHARP & DOHME

position, gasps, and puts her left hand to her back to hold or rub the site of the spasm. The shift in her body position, the gasp, and the gesture of moving her hand to her back are all operants.

Suppose for example, and it should not be difficult to imagine such a situation, a housewife had had much back pain in the past—perhaps a disc problem now resolved and producing minimal or no residual noxious stimulation. Suppose, further, making beds and similar heavy housekeeping chores had never been pleasant or rewarding for her. Her interests were in other pursuits. Finally, suppose that she has two teen-age daughters well steeped in helping with household chores. Given those conditions, when a spasm or some random pain stimulus from her back results in the protective operants and her daughters see the pain displays, they may step in. They may caution their mother not to do heavy work when her back hurts. They may take over to complete the task. When they do that, they have thereby delivered one or more potentially potent reinforcers. They have provided their mother with rest and the successful avoidance of pain. They have also provided the social reinforcer of displaying their regard, concern and readiness to help, which is a not unrewarding event for almost any mother. These are likely to be positive consequences. In this arbitrary example, they may be contingent on occurrence of the pain behavior. If there is no pain behavior, there is no stepping in to help. If pain behavior occurs, help and rest systematically follow.

The learning effect is automatic. The pain behaviors may come to occur without there being a spasm or some such noxious stimulus. It is not at all necessary to infer that the housewife makes a positive decision to pretend that she has pain so that her daughters will take over a noxious task. It is true that she could make such a decision and implement it by the display of pain behavior. But it is equally true that, given the systematic contingency arrangement specified and repeated over time, the housewife's conditioning could indeed occur. She could become incapable of discriminating that there was no longer a pain stimulus in her back when confronted with visual or symbolic cues indicating bed-making behavior should begin."[2]

Treatment of Operant Pain Syndrome

Evaluation to establish mechanisms of sick behavior and cause and effect of chronic complaint is difficult. Treatment depends on this evaluation process. A detailed description of treatment would have to be a subject of a second paper. Having described the problem and discussed the physician portion of evaluation, I can refer the interested reader again to Dr. Fordyce's book as the primary source of instruction and guideline for treatment. I would also recommend as required reading the books and articles listed in my reference list. I would emphasize two articles: (1) "Taking Care of the Hateful Patient" by James Rose, M.D., as published in the *New England Journal of Medicine*, April 20, 1978, and (2) the much older article by Hirschfeld, A.H. and Behan, R.C., "The Accident Process—Etiological Considerations of Industrial Injuries", *JAMA* 186: 193-199, October 19, 1963, with the second and third parts of this same title published in *JAMA* October 26, 1963 and July 11, 1966.

Because operant pain is defined as a chronic problem it demands some aspects of team approach. No one physician or psychologist can do all of the required treatment. The evaluation process will determine the contingent factors of behavior and identify the number of other people involved (including lawyers, insurance company adjustors, union bosses, work supervisors and family members, friends, neighbors, the minister, T.V. programs). A finished evaluation must be followed by a conference of the most involved people who come to some agreement and in some cases, develop a written proposal that the patient must then agree to before any treatment is to be undertaken. Because such a comprehensive program is not available in Maine, I would recommend that physicians do the best they can with what they have until such time as money is available to develop a specialized unit in this state.

Goals of treatment do not necessarily include return to work. The overall priority of goals in a treatment program are:

1. Reduction of health care services. This specifically means two separate problems:
   A. Elimination of narcotic drugs.
   B. Decreased visits and attention from the standard health care approach, medicine and surgery, physical therapy, and substitution with appropriate psychological counseling, on-going therapy with some minimal support from a physician for low-level symptomatic pain relief (Aspirin, Darvon® , occasional Tylenol® with Codeine, but never anything stronger than these three) and an effort to decrease time spent with all standard health care services (emergency room, rehospitalization, surgery, M.D. visits). These, of course, cannot be eliminated, but the direction is toward minimal utilization.
2. A coordinated in or out-patient program to teach and establish an altered behavior pattern and altered lifestyle directed toward some normalcy or at least some pleasure in life.

If the above treatment program is successful and the patient can enjoy some increased physical activity, the possibility of returning to work becomes a real one without any suggestion from physician, insurance company or lawyer.

Treatment Advice to Physicians

1. *TENS (Transcutaneous Electrical Nerve Stimulator)* TENS has followed acupuncture as the popular form of quick, easy pain control in cases that become problems to physicians. If a patient suffers from operant pain syndrome and has an abnormal

MMPI, TENS will usually give some temporary pain relief. In my clinical experience, when TENS is given to an in-patient suffering from chronic pain and the patient reports improvement in the complaint, one can expect a significantly abnormal MMPI result. TENS is useful for some types of acute organic pain, specifically, early forms of mild muscle spasm and the pain of post-op surgery in which a TENS can help reduce the amount of narcotic medication usually required after a surgical procedure. TENS may be used in the Emergency Room for acute muscle spasm.

2. *Activities Diary.* The patient can be instructed to keep a detailed, hour by hour record of his level of activity with his own estimation of pain (0-10), mild to severe, and the type of treatment including any modality, device or pill used at home. This is a useful technique for the physician in the sense that it reverses the role of the patient expecting the doctor to answer all questions and provide relief, and instead requires the patient to assume the responsibility of doing something for himself. Only until a physician or a psychologist has a detailed two-week diary can one decide what category or what type of problem exists in an individual case.

3. *Order the MMPI test.* Once the red flags of chronic pain begin to plague your office with no response to any attempt at treatment, and with a suspicion of exaggeration of discomfort or any question of secondary gain, the MMPI becomes more important than any other test. Laboratory studies for rheumatoid factor, sedimentation rate and uric acid, plus x-rays of the part of the body that hurts, must be done to prove that they are *normal.* The MMPI must also be done to prove that it is either *normal* or *abnormal*, and supports the impression by the physician that there is some psycho-social correlation with the superficial complaint of pain.

4. *Never tell a patient he does not suffer the pain he complains of:* Patients control their pain. There is no laboratory test or x-ray to measure pain. There is no way to measure pain threshold other than the indirect approach of MMPI testing to measure levels of anxiety, depression, hypochondriasis and psychoneurosis.

5. *Physical Therapy.* An appropriate trial of physical therapy should be limited to six to eight treatments by a physical therapist who is expected to take an independent history with examination of effected parts for range of motion and manual muscle testing. At the most, a patient might be referred to physical therapy for as many as twelve treatments, three times a week for four weeks. If there is no improvement or change in the patient's complaint over a period of two to three weeks, there is no point in continuing in the physical therapy department. Continuing will only tend to reinforce the impression that there must be something wrong, and yet no one can treat the problem; therefore, it must be worse than others. The same applies to patients who have complaint of pain, usually relating to the spine, who submit themselves to chiropractic or osteopathic manipulation two or three times a week, month after month. This is a form of physical therapy with the major benefit in the area of "laying on the hands." There is probably some relaxation effect and treatment of muscle spasms, but if marked improvement is not obtained after two to three weeks, at the most eight to twelve treatments, this should also be discontinued, since it cannot reasonably be expected to provide any relief after twenty to thirty treatments.

6. *Surgery.* Of all patients complaining of back problems, only 2% should come to surgery for degenerative disc disease, while 98% can be managed effectively on a conservative program. The extremely low figure of 2% requiring surgical correction is not a number proven by any statistical study that I am aware of; however, it is the opinion of most orthopedic surgeons who have had enough time and experience to estimate that only 1 out of 20 seen in their office practice ever requires any type of surgical procedure. The other 98% cannot be treated by ordering "take it easy," plus some medication. These patients should be referred to a physical therapy department with an interest in chronic back pain for a formalized, detailed program of instruction in back exercises and isometric muscle strengthening. The physical therapist involved should be able to first perform a mechanical back evaluation, using the muscle testing sequence described by Kraus-Weber.[3]

7. *Medication.* Medication such as Talwin® , Percodan® and Demerol® on an out-patient basis can only lead to a new and more serious problem of drug misuse. Drugs such as Talwin used in high doses on a chronic basis will cause symptoms of multiple sclerosis which fortunately are reversible.

8. *Rehabilitation.* Treatment for a long-term severe case of operant pain syndrome requires admission to a rehabilitation unit with an appropriate team approach in which the psychologist will take charge of the overall program, supported by physical therapy. This requires intensive psychological counseling to the patient, his family and any other associated concerned person who will be involved in his follow-up care. A program to deal with behavior modification must wait for adequate reduction of narcotic medications. The program must develop a system for behavior modification basically done by extinguishing bad behaviors and rewarding improved behaviors.

With the above understanding of this problem, I have enjoyed marked improvement in handling of these problems and the satisfaction of providing a new service at the Mid-Maine Medical Center for patients who can only waste the time of orthopedists and neurosurgeons. They, of course, waste a great deal of time and money for themselves and the taxpayer because of our present health system approach and the present laws governing the decisions in compensation of work-related or accident-related injuries. It is my hope that an organized rehabilitation program will be established in the State of Maine to provide the in-hospital and follow-up treatment for

rehabilitation of this category of patient.

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ACTINOMYCOSIS—*Continued from Page 52*

The secret of effective antibiotic treatment is to give large amounts for long periods of time in order to assure adequate sterilization of the necrotic and fibrotic inflammatory masses. Generally patients are treated with parenteral penicillin G 4-10 million units daily intravenously during hospitalization and then with tetracycline by mouth (500 mgm 4 times a day for adults) for 3-6 months or longer. As in other infections, it seems important to provide drainage by surgery when indicated.

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Annual Meeting Dates For Your 1979 Calendar . . .

Maine Medical Association, June 16-19

Treadway-Samoset, Rockport, Maine

American Medical Association, July 22-26

Chicago

Laboratory Testing for Antimicrobial Therapy

JOHN W. CHOWNING, M.D.*

There are numerous considerations involved in selecting an appropriate antimicrobial drug to treat an infection. These include a knowledge of the susceptibility of an infecting organism to an antimicrobic, the clinical pharmacologic properties of the drug, previous clinical experience in treating infections due to the infecting species, the nature of underlying pathological process and the immune status of the patient. Of these factors, the amount of antimicrobic required to inhibit or kill an organism in-vitro and the level of the drug obtained in body fluids during therapy can be directly measured by the clinical laboratory. This statement applies only to the testing of aerobic bacteria in most hospital laboratories. Fungi, obligate anaerobes and other slow growing organisms are not usually studied except in special investigative institutions because of the difficulties involved with these organisms. Because of changing susceptibility patterns, the Mycobacterium tuberculosis is routinely tested, and this is performed in the State Health Department Laboratory in many states including Maine.

Routine susceptibility testing is not needed when resistance has not been described for the antimicrobic of choice (i.e., Group A Streptococci and Neisseria meningococcus are uniformly sensitive to penicillin). Also, testing is not recommended on organisms which are very fastidious because the test results are not usually very accurate unless special procedures, not available to most institutions, are used. Examples here include the streptococci, except enterococci, and Neisseria gonorrhoeae, all of which are very fastidious. They are also generally susceptible to penicillin. Enterococci are usually resistant to penicillin, and should be tested. Some Neisseria gonorrhoeae are now showing penicillin resistance and this is on the basis of beta-lactamase production. These organisms should be tested with procedures for beta-lactamase production. Some pneumococci from South Africa have been described which are penicillin resistant and this is not on the basis of beta-lactamase production. To date, no case of penicillin resistant pneumococci has been described in the U.S.[1] However, this should be kept in mind for cases of pneumococcal infection which do not respond to conventional therapy. Presently, it is not recommended that the other streptococci, except enterococcus, undergo susceptibility testing because of their fastidious growth pattern in-vitro. However, a commercial procedure for performing the broth dilution susceptibility method on streptococci will soon be marketed so that testing will also be available for these micro-organisms when the need exists.[12] Susceptibility testing should be avoided on members of normal flora in their natural habitat and on organisms known not to be playing a pathogenic role. Such testing is wasteful and misleading. Urinary isolates should be tested for susceptibility if they are present in counts greater than 10^5/ml. However, cultures containing high counts of three or more organisms are probably contaminated. Also sputums containing many epithelial cells are probably not acceptable samples for testing because of the contaminating upper respiratory tract organisms which tend to adhere to epithelial cells.[2] Presently, susceptibility testing in most laboratories is performed by one of two methods, either the diffusion or the dilution method. Both of these methods have been standardized and approved by national organizations so that there should be good interlaboratory reproducibility if the standards are adhered to.[3]

The diffusion method is most widely used and dates back to the 1940's when filter paper discs were impregnated with penicillin to measure bacterial susceptibility. This has been expanded today to the point where an infecting organism is tested with several different antibiotic discs, with the antibiotics chosen on the basis of whether the organism is gram positive or negative. The filter paper discs containing fixed amounts of antimicrobics are applied to the agar surface which has been streaked with the organism to be tested just prior to the disc application. At the same time that the organism is multiplying logarithmically on the agar, the antimicrobic is diffusing into the surrounding media, with the concentration of antimicrobic diminishing as the distance from the disc increases. In this way, if the organism is susceptible, a zone of inhibition will occur where the concentration of antimicrobic is sufficient to inhibit growth of the organism. The diameter of the zone of inhibition relates almost linearly with the log of the minimal inhibitory concentration (MIC). The minimal inhibitory concentration is the concentration of antimicrobic which is necessary to inhibit growth of an organism in-vitro. Based on the knowledge of the pharmacokinetics of each antimicrobic and the clinical responsiveness of organisms, MIC zone breakpoints have been defined above which an organism should be considered resistant and below which it is considered susceptible. An intermediate zone exists between these two extremes to identify situations where the exact susceptibility pattern of an organism cannot be determined. The MIC breakpoints are related to blood levels usually expected with frequently used dose schedules, or to urine levels where a drug is used almost exclusively for urinary tract infections. The resistant and susceptible categories apply to systemic infections.

Testing in the diffusion method must be limited to pure cultures as mixed cultures produce inaccurate interpretations. However, several colonies of the

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same species from the plated specimen should be mixed together to form the pure colony preparation. In this way, if there are mutant strains present within the infecting organism group and they have different susceptibility patterns, they will be identified. Results with the diffusion method cannot be directly correlated with expected serum or urine antimicrobial levels because of the way the results are expressed (S, R or I). Also, because the "breakpoints" mainly correspond to serum levels, the method underestimates the antimicrobic activity in urine where the drug usually has a concentrated level as opposed to the serum.

The dilution methods directly measure the minimal concentration of an antimicrobial agent necessary to inhibit (MIC) or kill (MLC) an organism. The dilution methods can be performed either using agar or broth dilutions. In the agar dilution method, agar plates containing varying dilutions of antimicrobics are inoculated with the organism or organisms to be tested. The MIC is the titer of the plate showing inhibition of an organism. The killing concentration cannot be determined by this method.

The broth dilution exposes an inoculum of organisms to varying concentrations (usually twofold dilutions) of an antimicrobial agent during incubation. The MIC is the lowest concentration of drug that completely inhibits macroscopic growth. By culturing the tubes that show inhibition onto antimicrobial-free media, the minimum killing or bacteriocidal concentration (MLC or MBC) can be determined. The bacteriocidal agents are generally preferred in the treatment of bacterial endocarditis and infections occurring in the immunocompromised patient.[4] The results are usually expressed in a way that allows the antimicrobial concentration necessary to achieve the desired MIC in the blood or urine to be easily calculated. The dosage regimens include levels attained by oral application, levels attained by high systemic dosage, and levels attained in the urinary tract or locally.

In systemic infections, the dosage employed should give a peak blood concentration substantially higher than the MIC. This factor has been variously portrayed as two to five times the MIC and depends mainly on the protein binding of the antimicrobial.[8] The MIC in the blood should not drop below the required level of in-vitro inhibition before the next dose of antimicrobial reaches the blood stream. Other points to remember are that some organisms may appear to be susceptible to a relatively low MIC, such as Staphylococcus aureus to penicillin, but that because they produce beta-lactamase they should be considered resistant. Dilution methods do not detect beta-lactamase production. Also, just because an organism has a relatively high MIC to an antimicrobic does not mean that blood levels much higher than the MIC might not be achieved to which the organism might be sensitive. The toxicity of the drug may be the limiting factor in these cases.

In the past dilution methods have been cumbersome to work with, but with newer methodologies such as microtiter plates for the broth dilution method, this has become less of a problem. There are also automated procedures using these methods. However, all of these techniques are more expensive than the standardized diffusion method. They may also fail to detect resistant mutants or contaminated cultures. A potential advantage of the dilution method is the ability to test fungi, obligate anaerobes and other fastidious organisms. These organisms must be tested using special adjustments of the standard procedure and cannot be performed using most of the commercial components. Another potential advantage is the testing of combinations of antimicrobials, as these sometimes show synergistic or antagonistic activity. Again, these studies cannot be performed with the commercially available systems.

Some isolates of Staphylococcus aureus, Hemophilus influenzae and Neisseria gonorrhoeae are resistant to penicillin and/or ampicillin because they produce a beta-lactamase that inactives the antimicrobial agent. Several rapid tests are available for testing for beta-lactamase production and should be routinely ued on those organisms known to produce this enzyme. All of these tests are relatively simple to perform and should be performed in those laboratories doing microbiologic identification.[5,9,10,11]

On occasion, it may be necessary to obtain accurate measurement of serum concentrations of particular antimicrobial agents. These tests are generally performed on agents in which the margin between therapeutic and toxic levels is narrow, such as the aminoglycosides, or in patients with renal failure who accumulate agents which are normally excreted in the urine. It is especially important to collect the specimen at the proper time. In general, this should be immediately before the next dose to demonstrate that the in-vivo level is still above the necessary MIC, or at the point of maximal serum concentration where toxicity is a problem. Peak levels generally occur one hour after an intramuscular injection or directly after an intravenous dose. With continuous intravenous therapy, the sample may be obtained at any time.[7]

The most commonly assayed drug is gentamicin. A recent study demonstrated that most tests for gentamicin were improperly ordered and the results were poorly utilized.[6] In general, patients receiving this drug should have an assay to verify an adequate dose schedule, and renal function should be monitored every two to three days with appropriate laboratory tests.

The measurement of serum bactericidal activity (Schlichter test) is another means of assessing whether antibiotic therapy is sufficient. Samples of the serum of treated patients are incubated (in doubling dilutions with broth) with the infecting organisms to determine the highest dilution showing no growth of the organism. In this manner, the combined effects of susceptibility of the infecting organism and serum concentration of antibiotic can be indirectly

measured. The method has been suggested as a guide for the treatment of bacterial endocarditis and other complicated clinical situations. In endocarditis, the usual feeling is that titers of 1:4 to 1:8 are needed to successfully treat the patient. This has never been confirmed in an adequately designed study. However, it may provide a measure of confidence if the clinical course is statisfactory.[4]

Summary

The in-vitro testing of infectious organisms offers a meaningful adjunct to the clinical assessment of therapy in the ill patient. The diffusion method is still the most widely used method and in many cases provides as much information as is needed. The dilution methods provide more precise information and can be useful in the treatment of systemic disease, deep wounds and meningitis. It should be remembered that the MIC is the minimal concentration inhibitory to the infecting organism. The serum or urine dosage regimen should allow an MIC two to five times the MIC determined by in-vitro testing to keep the levels of antimicrobial agent adequate for therapy. Direct serum levels may be obtained to determine if the MIC is being kept in the useful range for an antimicrobial agent or to determine if the toxic level of the agent has been reached. Indirect measurement of serum bactericidal level can also be performed on cases where the clinical situation justifies this procedure.

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Philosopher to Pediatrician

EUGENE PETERS, M.D.*

"Marvel not then at the love which all men have of their off-spring; for that universal love and interest is for the sake of immortality."
Plato, Symposium *208 (Jowett trans.).*

Ever since Plato philosophers have digressed on children, usually in reference to child-rearing—so much that philosophy of education has become a philosophical subspecialty. John Dewey achieved his own immortality in the pantheon of American educators; and Jean Piaget, who draws heavily from the philosophy of phenomenology, may have already attained a similar status in child development. Many philosophers, professional academicians, feel vaguely discomfited that their ideas should have "cash value" (John Dewey's phrase), despite the strong traditional philosophic interest in human beings prior to the age of reason. Plato views neonates as having desires but lacking reason, which is gradually acquired—hence his interest in education. In the history of Western thought, children have attracted considerable derivative philosophic attention, mostly in the context of education. Since the majority of philosophers have invested themselves heavily in education (are there philosophers who are not professors of philosophy?), this outcome might have been anticipated.

What of the philosopher who is interested in children as more than potentially reasoning beings? He becomes a pediatrician.

The journey from philosophy to pediatrics may be distant but need not be harsh. Besides, distance is relative; it depends on one's point of view. Philosophers and pediatricians resemble one another in many respects. Both are reputed to be interested in little things, subtle signs and distinctions, subjects representing a minority of society's energies; both devote a significant portion of their time to instruction; and both are accustomed to relatively limited remuneration.

What has philosophy to do with medicine or medicine with philosophy? Currently the immediate answer is: medical ethics, inadequately characterized as a quagmire in search of victims. Few professionally trained philosophers have had clinical experience in medicine, and practicing physicians are rarely trained in philosophy. Hence, discussions of medical ethics typically blend the abstractions of the inexperienced with the confusions of the philosophically illiterate. Though we may learn to use moral language at mother's knee, mother is usually not a philosopher. And that is probably a good thing. The ambiguities and complexities of the moral issues physicians encounter overwhelm the exactitude of contemporary philosophers, who express themselves as readily in language drawn from mathematical logic as in ordinary discourse. Perhaps medical practice and professional philosophy differ most strikingly in the inexactitude of the former and the precision demanded in the latter.

How then do philosophy and medicine impinge on one another? As a former teacher of philosophy, now a pediatrician, I find noteworthy the amount of time devoted to teaching in the practice of generol pediatrics. Parents, especially new ones, are often apt students. They are strongly motivated, have an immediate interest in the subject, and respond with good humor and alacrity to a sufficiently relaxed instructional environment. This one-on-one form of education delights an inveterate teacher as naturally as a colicky baby elicits grandmotherly advice. As a final fillip for the teacher, this course requires no examination, no papers, and no grading. Even Socrates might be envious.

Teaching parents offers two special challenges: attitudes are to be transmitted as much as information, and parents must be taught without the appearance or paraphernalia of formal instruction. How the pediatrician approaches the child can be a model for the parent just as much as a classroom teacher can be a model whose influence on his pupils reaches far beyond the classroom and the subject matter. Most of us remember the painful boredom and tension endured from time to time in the enforced, obligatory education of which we were all prisoners. Therefore, the pediatrician as teacher will scrupulously avoid formalizing his instructional efforts and evoking those wrenching memories. Pontificating and routine lecturing recall those lovely spring days when the windows in the classroom were open, the trees were leafing yellow-green, and the teacher drones on endlessly to inattentive victims invisibly bound to hard wooden chairs.

Pediatrics and philosophy meet in the art of practice, whether of medicine or of teaching. As a teacher, I doubt my style has changed much from philosophy to pediatrics. In these days of data processing, the art of medicine is often smothered by the overwhelming bulk of the science of medicine. The laboratory at times threatens to swallow us all. Grateful as we are for laboratory medicine, the practice of pediatrics revolves ultimately around human beings. People may be the object of the tests ordered; but they are also subjects engaged in a personal exchange with the physician. Students are likewise engaged by a good teacher. Chaucer's description of the Oxford scholar might apply to the complete pediatrician: "Gladly would he learn, and gladly teach."

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Conduction Aphasia

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Aphasia is a disorder of cerebral function resulting in an impairment or loss of previously existing language abilities. As such, it is to be differentiated from dysarthria which is a disturbance of articulation secondary to central or peripheral nervous system or end-organ disorders and in which no abnormality of language itself is present. In addition, aphasia is to be distinguished from delirium and dementia which are more global impairments of cerebral function including memory, orientation, self care, etc., as well as language functions.

The locus of language function appears to be the left hemisphere for nearly all right handed individuals and for perhaps 60% - 80% of left handed ones. Although aphasia may occur as a consequence of any lesion capable of injuring the brain, the most frequent causes are cerebrovascular disease, trauma, and tumors. The acute onset of an aphasic disturbance in an older individual is in the majority of instances due to cerebrovascular disease. The recognition of the aphasia together with a diagnosis of its type will also lead to a localization of the cerebral lesion and aid in the work-up of its etiology. The case reported here represents one of the classical aphasic syndromes.

Case Presentation

This 83-year-old right handed male was admitted to the Mid-Maine Medical Center on 2/5/78 because of progressively worsening cough, anorexia, nausea, and vomiting over a one week period. His past medical history included the presence of mild chronic obstructive lung disease, the past occurrence of a myocardial infarction, and occasional episodes of angina pectoris. There was no prior history of neurological symptomatology. On admission, there was clinical and radiological evidence of pulmonary congestion. The patient soon went into respiratory failure and was treated for what was felt to be a combination of bilateral viral pneumonia and acute congestive heart failure. On 2/10/78, when his respiratory status had much improved, it was noted that he had speech difficulty unassociated with any other neurological deficits. The speech disorder seemed isolated to the production of individual words or parts of sentences, and did not seem to interfere with his understanding or ability to produce some grammatical sentence structure. On 2/15/78, a neurological evaluation revealed the patient to be an awake, alert, cooperative individual with fluent, paraphasic speech. He followed single and double (also known as "two stage") commands with occasional right/left confusion. He was able to repeat some "overlearned" sentences (e.g., "How are you?") but could not repeat more meaningful or novel 3 word sentences or phrases. Cranial nerve examination revealed a dense right, inferior quadrantanopsia. Sensory examination revealed a dense loss of the cortical sensory functions of stereognosis and position sense in the right upper extremity and of position sense in the right lower extremity. Motor and reflex examination were normal. Babinski responses were absent.

On 2/23/78, a bedside speech and language evaluation was performed using selected items of the Boston Diagnostic Aphasia Examination.[1] The patient's fluency of speech fluctuated. Fluency for social speech was grossly satisfactory. Propositional speech contained occasional fluent, clearly articulated phrases with normal prosody; however, these phrases were separated by numerous non-fluent literal paraphasias (responses containing deletions, additions and/or transpositions of the sounds composing the target word). When these paraphasias occurred, he usually attempted to self correct the error, and each attempt often successively approximated correct production of what he wanted to say. His production did not improve by having the examiner cue or provide a model of the target word. Numerous verbal paraphasias (word substitutions) and neologistic paraphasias (neologisms) were also present.

Auditory comprehension was mildly depressed, however, superior to oral verbal output. Responses were generally complete for three stage auditory commands. Responses to yes/no questions were accurate. The patient could point to body parts upon request. He demonstrated right/left confusion. He pointed to pictures of common objects, simple geometric designs and to printed capital letters upon request with approximately 80% accuracy. Often, he appeared frustrated by his difficulties with oral communication.

Fluency in repetition tasks was disproportionately lower than fluency for conversational speech. The patient successfully repeated a few one syllable words. On two occasions, he successfully repeated three word social phrases. Attempts to repeat polysyllabic words and phrases were characterized by literal and verbal paraphasias. As the length of the word or phrase to be repeated increased, his responses further deteriorated. Repetition for monosyllabic numbers was intact, however, he could not repeat bisyllabic numbers without paraphasic interference. When words were combined with those numbers he could repeat (e.g., the phrase "4 plus 4 is 8"), his previously correct responses again were contaminated by paraphasic errors.

Mean length of response was probably 4 with a range of 1 to 7. He demonstrated a variety of grammatical structures. Speech was appropriate to the situation. He named several pictures of common objects with paraphasic errors. Fluency and articulation did not improve in singing attempts. Reading and writing abilities were severely depressed. Attempts to read words resulted in paraphasias. Attempts to write his name were unintelligible. Voluntary control of the oral mechanism for non-speech tasks (protruding the tongue, swinging the tongue from side to side, etc.) was satisfactory.

During the course of his hospitalization, the patient exhibited a modest improvement. On re-evaluation five weeks later, his speech had become more fluent. Mean length of response had increased to 5 with a range of 1 to 10. Literal, verbal and neologistic paraphasias remained. He could repeat most one and two syllable words without paraphasic interference. He successfully repeated a five word phrase. Attempts to repeat other polysyllabic words or phrases resulted in paraphasic errors. He repeated numbers well, but still could not combine them with words.

Discussion

In clinical practice, the sudden onset of a speech disturbance in a middle-aged or older patient should bring to mind the possibility that this represents an aphasia. The next step in the clinical evaluation is to determine whether there is a language disorder, to define certain of its characteristics, and at the same time by evaluating the patient's more general mental and physical functions to exclude the existence of an acute dementia or dysarthria.

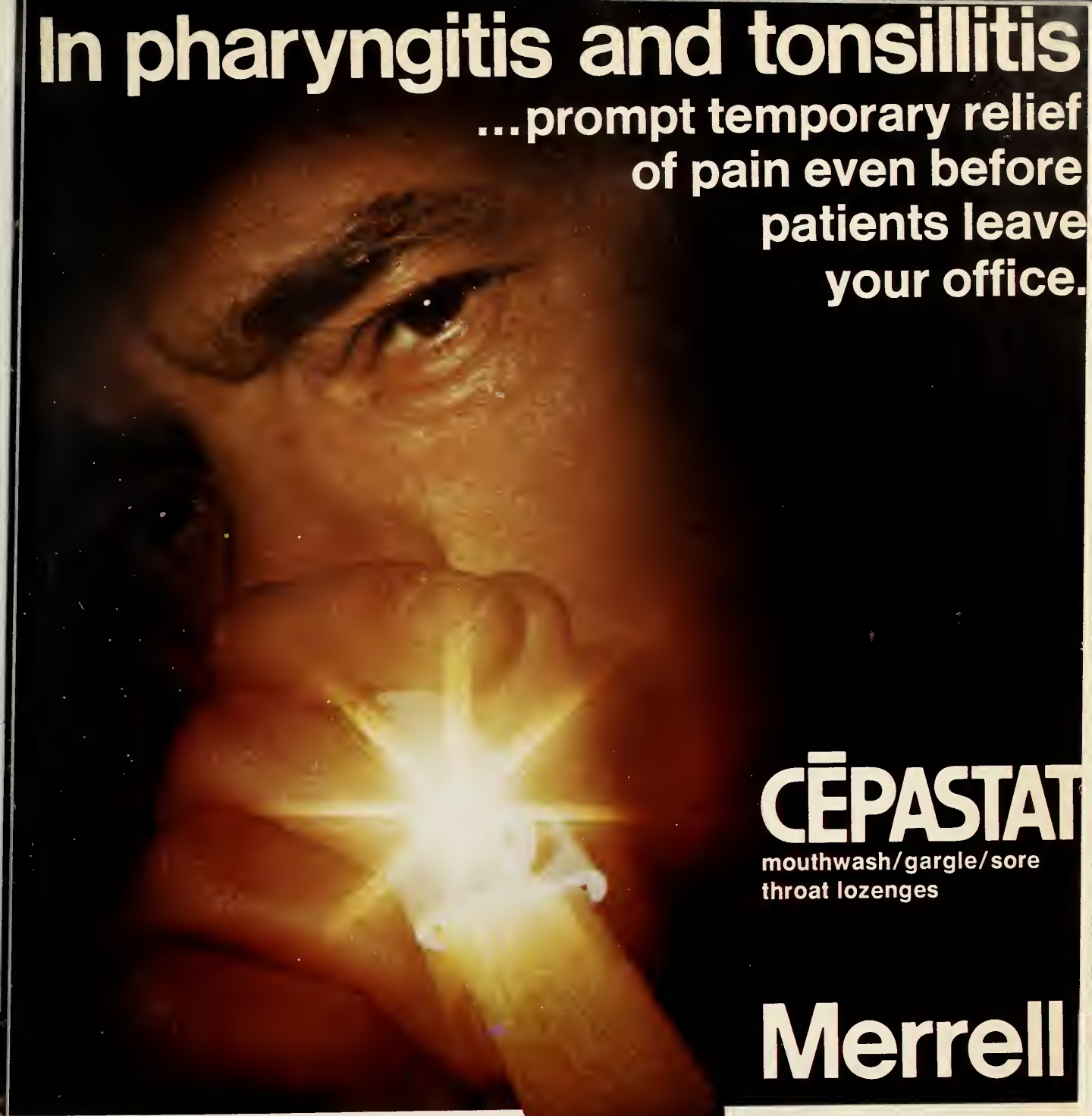
Over the years a number of somewhat different schemata for classifying the aphasias have been suggested. These generally have been based on the dichotomy of expressive/receptive language dif-

Continued on Page 65

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When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

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ficulties and are rooted in the two classical examples of each, Broca's and Wernicke's aphasias. Operationally, however, it has become more appropriate to base classifications on a series of individual items on which the patient can be tested. A simplified version of these items are presented below.

Spontaneous speech is the first item assessed. Is the patient demonstrating fluent or non-fluent speech? Determine whether there is a good rate of output with normal tone, inflection and grammatical construction. The patient may instead have non-fluent speech consisting of few words, poorly articulated, spoken with much effort and grammatically incomplete (referred to as "telegram-like speech"). Speech may be relatively fluent but characterized by paraphasia. This refers to the substitution of inappropriate or unintended words or sounds during speech. It comes in two varieties: 1) literal or phonemic paraphasia in which an incorrect sound is spoken as the patient attempts to produce a word ("sty" instead of "tie" when referring to a necktie), and 2) verbal or semantic paraphasia in which a correctly spoken but contextually incorrect word is substituted in speech (referring to a "wrist-watch" as a "time").

Comprehension is tested by giving the patient commands. This may have to be done in more than one manner if the patient appears to fail at first since it may be his output for following the command (either verbal or motor) which is at fault rather than his receptive ability. Tests include having the patient point to named objects in the room or to body parts, perform actions with his limbs, and answer questions. The latter might be done with questions requiring just a "yes/no" response in those patients who can produce the words reliably.

Repetition is easy to examine. Start with one syllable words and with familiar, "overlearned" material (e.g., "Good Morning") then progress to more difficult words and phrases, the ultimate in terms of difficulty and conciseness being a phrase like "No ifs, ands, or buts." This area is probably the one most often neglected in the casual examination of the aphasic. Repetition may be impaired in many aphasias including those with disorders of fluency and comprehension, but when it is selectively impaired without major disturbances in these other areas, it is virtually diagnostic of conduction aphasia.

Naming or word finding ability is the final item to be assessed in the brief examination. It is tested for by presenting or pointing to various objects or parts of objects in the room or on the examiner's or patient's person (e.g., watch, watchband, belt buckle, etc.) and having the patient name them. This test is difficult for most aphasics but is of interest, in part, because it occasionally occurs as an isolated disturbance (anomic aphasia) with preservation of fluency, comprehension, and repetition.

With the four above items tested, one can roughly categorize patients into the major aphasic syndromes (Table 1).

TABLE 1

CLASSICIATION OF THE APHASIAS. NOTE THAT THE ISOLATION AND TRANSCORTICAL MOTOR APHASIAS ARE INDICATED TO BE NON-FLUENT BUT WITH INTACT REPETITION. THESE PATIENTS ARE NON-FLUENT WITH RESPECT TO SPONTANEOUS SPEECH BUT CAN REPEAT WHAT THEY HEAR SPOKEN. (+) REFERS TO PRESERVED FUNCTION; (0) REFERS TO IMPAIRED OR ABSENT FUNCTION.

	Fluency	Comprehension	Repetition	Naming
Broca's	0	+	0	0
Wernicke's	+	0	0	0
Conduction	+	+	0	0
Anomic	+	+	+	0
Isolation	0	0	+	0
Global	0	0	0	0
Transcortical Motor	0	+	+	0
Transcortical Sensory	+	0	+	0

The patient whose communication disorder was presented above represents a classical picture of conduction aphasia.[1] He exhibited fluent conversational speech with normal grammatical structures and normal rhythm, intonation, and melody (prosody). He had good auditory comprehension. There was a marked impairment of repetition ability with, as has been reported, a relatively better preserved ability to repeat numbers as opposed to words.

Our patient's speech was marked by numerous literal (phonemic) paraphasias with repeated attempts to correct them. In some conduction aphasics, the severity of the paraphasic speech and associated attempts at self correction can induce an appearance of non-fluency which makes the speech pattern similar to that of Broca's sphasia. It has been pointed out, however, that the two aphasias differ in the following ways: 1) the articulation of a Broca's aphasic usually improves with a model from the examiner whereas the conduction aphasic's articulation does not, and 2) the conduction aphasic demonstrates a variety of syntatic patterns whereas the hallmark of a Broca's aphasia is agrammatism. Both of these differentiating factors were true for our patient although his speech was fluent enough so as not to be confused with a Broca's aphasia.

As in most areas of neurology, the interest in classification of the aphasic disorders stems from attempts to elucidate structure-function relationships in the brain. The original case studies of Broca and Wernicke determined that lesions of the posterior portion of the inferior frontal gyrus related to expressive or non-fluent aphasia, and that lesions of the posterior portion of the superior temporal gyrus related to disorders of comprehension. Over the years additional data have been accumulated which define the theoretical anatomical bases for all the aphasias listed in Table 1. A lesion of the white matter pathway known as the arcuate fasciculus which connects Wernicke's and Broca's areas (i.e., from posterior temporal to inferior frontal lobe) is the basis for conduction aphasia. One can conceptualize

the situation as follows: the preservation of Wernicke's area allows for preserved comprehension, the preservation of Broca's area allows for fluent speech, but the disconnection between the two interrupts repetition.[2]

The availability today of radionuclide and computed tomographic (CT) scanning allow for anatomical localization of lesions not previously possible in the living patient.[3,4] These studies (see Figures 1 and 2) were performed in our patient and served two important functions: 1) define the nature of the patient's pathology which given the clinical situation could have been a developing abscess (less likely a neoplasm) even though statistically it was most likely a "stroke," and 2) provide anatomical correlation with the clinical picture which in this case is quite good. One might note also that the primarily deep parietal location of the lesion is well correlated with

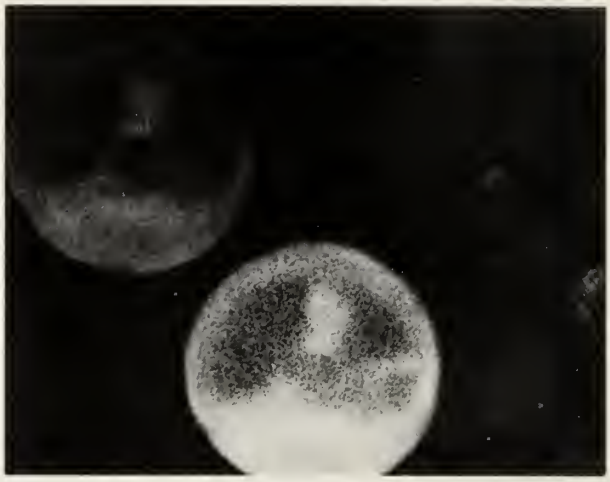


Fig. 1. Radionuclide brain scan (left lateral view) showing abnormal area of increased uptake in the anterior parietal lobe.

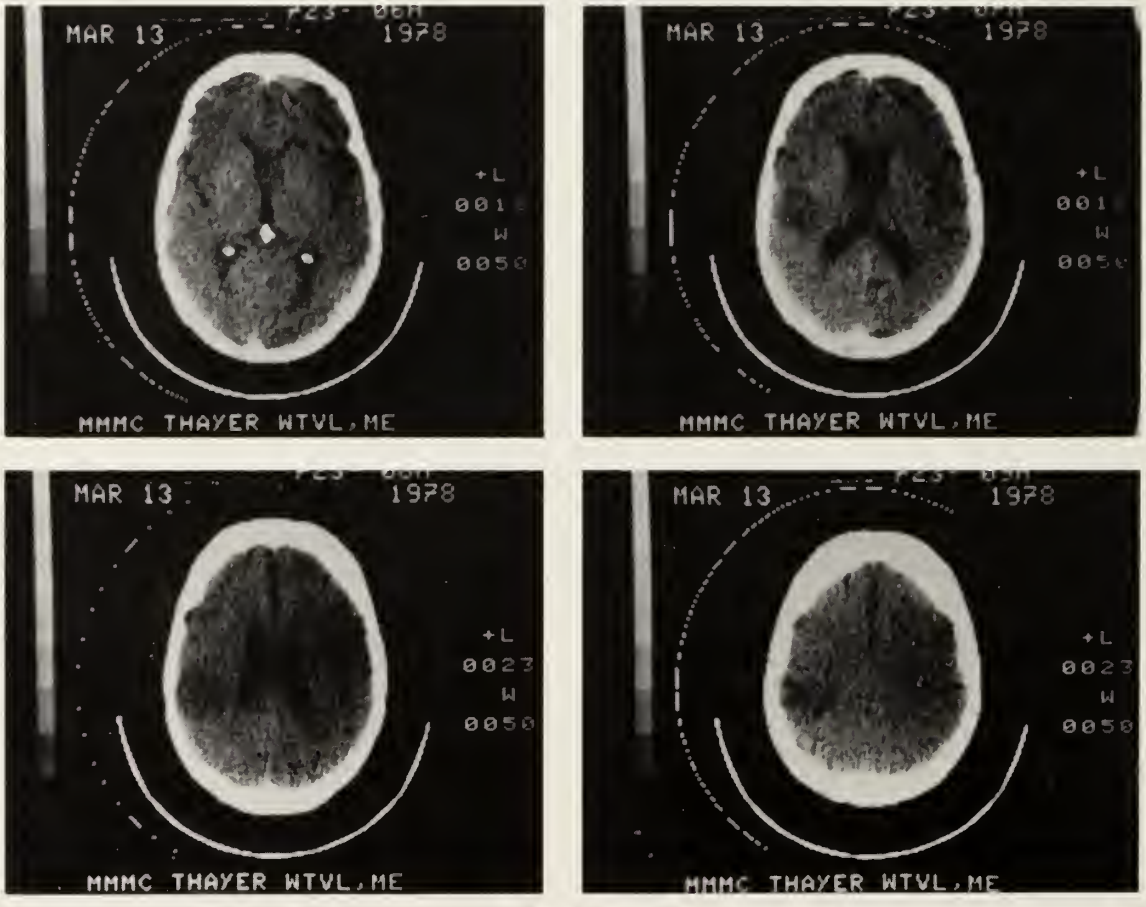


Fig. 2. Computed Tomographic (CT) scan of the brain showing four sequential "cuts" from inferiorly to superiorly (labeled 06 through 09) and revealing an abnormal lucent region in the (L) parietal lobe. This scan was done without contrast enhancement.

the clinically observed right, inferior quadrantic field deficit and the right sided cortical sensory defect.

Finally, the ability to specify the type of aphasic syndrome which a patient exhibits does have some prognostic importance. This is of course primarily true for that majority of aphasics whose disorder is the result of a cerebrovascular accident or trauma and not due to a tumor or other progressive brain disorder. As might be expected, younger patients tend to recover more than older ones, and post-traumatic aphasias do better than those secondary to cerebrovascular disease. Among the various aphasias the global do poorly, the Broca's and Wernicke's do

Continued on Page 70

Computer Assisted Analysis of Raw Scores From the Porch Index of Communicative Ability*

Randall R. Robey, M.A. and Bruce D. Olsen, Ph.D.**

Porch (1967) introduced the Porch Index of Communicative Ability (PICA) as a standardized test of asphasia with high test-retest reliability and high inter-scorer reliability. This stability has earned the PICA widespread acceptance as a clinical and research tool among speech pathologists. The test consists of 18 subtests each containing 10 items. Each item relates to one of 10 common objects used throughout the test. The patient is required to relate to these objects through several modes of communication, e.g., talking, listening, reading, writing and gesturing. The test uses a 16 point multidimensional scoring system to describe a patient's communication behavior. This scoring system provides a standardized measure of changes in communication behavior over time. A unique characteristic of the PICA is its prognostic capacity. Normative data predict recovery to six months post onset of cerebral insult.

As with many tests, the PICA consumes time in four areas: administration, scoring, analysis and interpretation. PICA administration time ranges from 22 to 143 minutes (Porch, 1971). The test is often scored from a videotape recording making scoring time equal to or greater than administration time. Analyzing and interpreting scores are also time consuming processes. In our center, analysis time ranges from 20 to 45 minutes.

Knox (1975) introduced the concept of using computers to reduce PICA test analysis time. He developed a computer program for calculating predicted levels of communication functioning using point-slope intercept equations. Voeks (1977) expanded the application of this concept by developing a similar method for calculating percentile scores for six of the mean scores obtained on the test.

Both of these programs are limited in terms of input and output capacity. They accept only derived scores (means or percentiles) which must be hand calculated. The combined output of these programs is limited to six mean scores, their respective percentile values, and to the predicted percentiles.

This project was undertaken to reduce PICA test analysis time via a computer program capable of accepting raw scores and calculating the commonly used derived scores for test interpretation.

The program was written in FORTRAN IV (WATFIV) via a terminal/computer telephone hookup with the University of Maine at Orono Computer Center. The following is a description of the input/output characteristics of the program.

The 180 raw scores, minutes spent on each subtest, and the starting and finishing times must be typed into the program. The program calculates the 24 means associated with the test and searches the appropriate tables of norms (left hemisphere or bilateral damage) for each of their percentile values. Predicted percentiles for six months post onset are computed. Total time and the time spent on each subtest are compared to the mean lengths of time consumed by the asphasic sample described in the test manual (Porch, 1971). The subtest means are rank ordered. Subtest means are examined for patterns characteristic of bilateral cerebral sites of lesion.

In order to compare test results over time, the program is designed to ask the operator for scores of previously administered tests. A form was developed to organize this information for easy input. This form is completed by the clinician. Given this form and the score sheet, a trained secretary can assume the responsibility of typing in the data. Therefore, the time a clinician usually spends analyzing scores can be otherwise scheduled.

The program provides two primary advantages to the speech pathologist and the referring physician: speed and accuracy. The necessary data can be typed in and results obtained in approximately 8 minutes. Human error in mathematical calculation and in searching the tables of norms is eliminated. The program also has research value. It provides a consistent method for data gathering. Most likely, the program can be modified to examine test scores in whatever manner an investigator may be interested.

Copies of the program are available upon request.

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*Condensation of a paper presented before the American Speech and Hearing Association in San Francisco, CA, November 19, 1978.

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Argon Laser Treatment of Retinal Holes

Robert J. Takach, M.D. and Richard H. Dennis, M.D.*

The purpose of this paper is to describe and discuss the unique usefulness of the Argon Laser in helping to prevent the potentially blinding condition of retinal detachment. A short summary of 33 patients so treated in the Laser Laboratory of Mid-Maine Medical Center will be presented. These cases demonstrate that it is possible in some early cases to prevent a detachment, if the pre-detachment symptoms are recognized early, and treatment can be instituted at once. These symptoms are usually quite prominent and remarkable to the patient. They consist largely of sudden appearance of flashes of light and/or floating opacities in the field of vision.

The genesis of a detachment must be understood in order to comprehend the cause of these symptoms. The retina separates or detaches from the underlying tissues because fluid from within the eye has managed to get behind the retina through a retinal hole and peel it off. In order for this to occur, there has to be some break in the retina to allow passage of this fluid. This break may be a hole as a result of retinal degeneration in older people; it may be a result of trauma with a tear being made in the retina. A major cause of retinal holes is a contraction of the gel-like vitreous which fills the entire eye and which pulls a hole in the retina. The vitreous presses against the retina, helping to hold it in position. As we get older, the vitreous tends to liquify and contract, pulling away from the retina, so that it no longer acts as a support. Sometimes in pulling away, the patient experiences sudden appearance of spots and flashes of light. These are the result of traction on the retina by the adherent vitreous. If the vitreous attachment to the retina has been a firm one, it may pull off a small piece of the retina in contracting, thus creating the dangerous hole. The symptoms are remarkable enough so that the patient usually seeks some sort of medical advice. It is imperative that these cases be examined thoroughly in order to determine if a hole has been created. If it has, the patient will surely experience a detachment in time; therefore, this requires treatment at once.

If there is a hole in the retina, it must be treated in some manner to seal off the edges, to prevent fluid from getting behind the retinal tissues. Sometimes these holes will be discovered in the course of a routine eye examination. This is so in cases where there has been a gradual deterioration of the retina, producing a hole, and where there have not been symptoms. However, holes frequently are seen after the patient complains of the bright flashes and spots in his vision. These patients must be examined carefully when they present with such symptoms. If

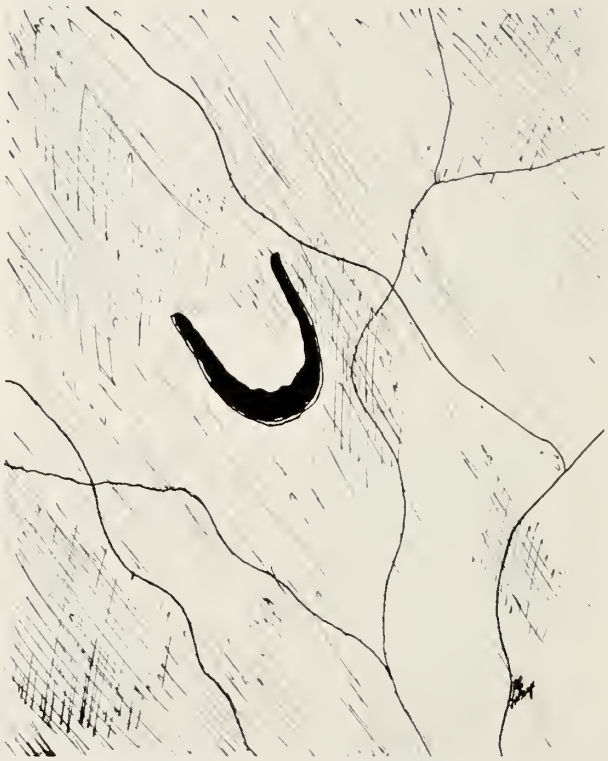


Fig. 1. Horseshoe retinal hole in peripheral retina before Laser treatment.



Fig. 2. Horseshoe retinal hole (tear) in peripheral retina one week after Argon Laser treatment. Chorio-retinal scars are observed as pigmented spots.

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Table 1

Total Cases	Male	Female	Age Range 20-39	40-49	50-59	60-69	70-80	Symptoms Flashes Spots	No Symptoms
33	13	20	2	3	8	15	5	29	5

Table 2

	Type of Hole Horseshoe	Round Holes	Number of Laser Treatment Sessions Per Hole					Cryotherapy Along With Laser
Superior Temporal	19	10	1	2	3	4	5	2
Inferior Temporal	3	1	18	10	7	4	1	
Superior Nasal	2	2						
Total	24	13						

Table 3

New Retinal Holes Discovered in Same Eye on Follow-up Visit	New Hole Other Eye	Limited Detachment Present Before Treatment	Subsequent Retinal Detachment After Laser RX
3	1	3	1

the hole is not treated and a detachment occurs, then of course, a serious and extensive operation is necessary to attempt to bring the retina back into position. While the results of the modern scleral buckle are quite good, it is obviously better to prevent the detachment entirely by early care of the hole.

There have been several reports on the incidence of retinal detachment following retinal holes or breaks. Davis[1] followed 212 eyes, 11/32 with symptomatic retinal holes detached; 20/183 eyes with asymptomatic holes detached. After cataract surgery, 50% of eyes with retinal holes detached. Shea[2] treated 48 eyes with symptomatic horseshoe tears and withheld treatment from 30 similar cases. Only 4% of the Laser treated retinas detached. Forty-eight percent of the untreated retinal holes results in detached retinas.

Many methods have been utilized to try to seal off the hole. They all employ the formation of a small scar made in a ring fashion around the hole. This scar bonds together all of the coats of the eye so that the fluid inside the eye cannot get between the layers. Early in the history of the treatment, simple heat was used. These were point sources and were applied to the sclera from without. This, of course, necessitated an operation but in many instances, the resulting bond from the scar tissue did prevent the inflow of fluid. When photocoagulation was developed, it was found that the heat produced by intense light focused on the retina could likewise produce a scar. At first, a strong white light, such as could be focused from a carbon arc, was used. As monochromatic light, such as the Laser, was developed, it was found that this was eminently useful because it was more controllable and easily applied. It is the Argon Laser which is most often employed now in sealing off these holes.

A total of 33 patients treated with the Argon Laser in our Laser Lab is reported here.

Results

As noted in Table 1, most of the patients treated were in the 50-80 year range (28/33) and most presented with symptoms of flashing lights or spots (29/33). When vitreous separation and retraction occurs in one eye, it likely will occur in the other. On one symptomatic eye, no hole was found, while in the other fellow asymptomatic eye, a large retinal tear was discovered. The point here is that both eyes should be carefully examined by the Ophthalmologist when the patient presents.

Table 2 lists the number of types of holes seen. Horseshoe tears (Fig. 1) are more likely to be symptomatic and are generally more dangerous. A horseshoe retinal tear appears as a flap of retina torn free from the surrounding retina by the vitreous retraction. Fig. 2 shows a horseshoe tear after Laser treatment with multiple Laser "burns" completely surrounding the hole. It takes several days for the Laser lesion to cause a chorio-retinal scar. This scar binds the retina to the underlying choroid and prevents fluid from within the eye from separating the surrounding retina. It may take more than one Laser treatment session to be sure the hole is closed (Table 2). If the hole is in the far periphery of the retina, cryotherapy is used to supplement the Laser treatment.

The treated areas must be followed closely as detachment can still occur. In a study by Robertson and Norton,[3] 13/301 eyes detached after initial treatment. In our series, one retinal detachment occurred

and required surgery following Laser treatment. This was one of our early cases and was probably due to inadequate Laser treatment.

On follow-up visits, the entire peripheral retina must be watched because new holes may appear. We observed new holes in the treated eye in 3 cases (Table 3). These occurred within the first two months after vitreous symptoms began. We observed the development of one new hole in the opposite eye.

Follow-up time on these patients ranges from one month to four years four months with the patients fairly evenly distributed over this time period. Pre- and post-op Laser visual acuities have remained essentially unchanged.

Summary

Thirty-three patients (37 retinal holes) have been treated with the Argon Laser in an attempt to prevent retinal detachment. The results have been good with only one subsequent detachment.

We recommend the referral of patients complaining of the sudden onset of flashing lights, spots, or floaters to an Ophthalmologist. Prompt detection of retinal holes treatable by Laser beam can prevent a visually debilitating retinal detachment.

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Conduction Aphasia—*Continued from Page 66*

moderately well, and the anomic, transcortical and conduction aphasics do best.[5] Much of the improvement is felt to be spontaneous. It remains a matter of controversy as to what extent speech therapy is beneficial in aiding recovery. There are few studies which clearly document the efficacy of speech therapy compared to the spontaneous patterns of recovery. Most writings on aphasiology, however, recommend speech therapy be provided.

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Renal Papillary Necrosis

William A. Greenlaw, M.D.*

Synopsis

The pathogenesis of renal papillary necrosis may involve diabetes, infection, obstruction, drug or alcoholic abuse, sickle cell disease, or renal transplant rejection. The treatment may be medical. The surgical treatment is aimed at relief of obstruction and control of threatened exsanguination. A case of unilateral renal papillary necrosis with threatened exsanguination is presented. This seemingly is a second such case for reporting in the literature.

Papillary necrosis, which, previous to 1905, was considered a rare kidney disease, is being diagnosed with increasing frequency. The pathogenesis is not clearly understood but it is apparently associated with ischemia.[7] Diabetes,[3] upper urinary tract obstructive uropathy,[3] consumption of large quantities of analgesics,[1,8] chronic alcoholism,[4] sickle cell disease,[5] and acute pyelonephritis[3] have been described as being associated with this disease. Tuma, et al[11] describe papillary necrosis in a renal graft. If there is no renal infarction, a benign clinical course may be encountered. At other times, infection may result in severe toxicity.

Two types of papillary necrosis are usually described. Sloughing of the entire papilla from the medulla may be noted. This papilla may pass into the calyx and disintegrate. At other times, it may move distally thereby producing obstruction. Occasionally it passes into the bladder and is passed on urination. The second type is the medullary papillary necrosis. In this situation, the necrosis spreads from the papilla into the medulla. Clinically, a benign course may ensue. There may be no symptoms. Signs and symptoms of obstruction of the ureter with no bacteruria may be noted. The urine may contain moderate amounts of red blood cells. Sterile pyuria might be observed and hematuria can be the only symptom. Various grades of infection from mild pyelonephritis to septicemia may ensue. As a rule gram negative organisms are the cause of septicemia with shock.

A critical review for drug abuse, alcoholism, diabetes, and sickle cell anemia must be undertaken. Evans[3] reports a patient with papillary necrosis who denied every possible symptom associated with any cause and effect of papillary necrosis.

Most frequently the diagnosis is made by retrograde pyelogram. If the papilla has sloughed, a concavity is demonstrated in the papillary area of the calyx. A non-opaque area is noted on pyelography if the papilla is lodged in the pelvis of the kidney or in the ureter. Renal tuberculosis, papillary sclerosis, or simple vascular ischemia must be differentiated with these films. Renal venous thrombosis and previous renal infarcts must be differentiated from this disease.[10]

The medullary papillary necrosis is demonstrated by the sloughed core filled with contrast material from the tip of the papilla to the medulla. Pocketing of the contrast material may be noted in the medulla. This may extend into the pyramid and is characterized by its irregular edges. The defect does not arise from the calyceal fornix as does the calyceal diverticulum. Excretory urography is usually limited by little excretion of the dye from the involved kidney.

Papillary necrosis is treated both medically and surgically. Medically, avoidance of etiological agents, control of sepsis, fluid and electrolyte management is mandatory. Obstruction by a papilla or clot must be relieved surgically. Cystoscopy and passage of ureteral catheters may relieve the calyceal pressure.[9] Ureteral catheter loop or stone basket may be used to remove any papilla lodged in the ureter. Appropriate antibiotic therapy must be initiated for control of bacteria and sepsis. Successful renal revascularization may result following the above treatment. Gulfronson, et al[6] report renal revascularization after thirty days of renal artery obstruction. Uncontrollable hemorrhage, obstruction, and sepsis may necessitate partial or complete nephrectomy. Transient dialysis occasionally is indicated as mentioned by Berning, et al.[2]

Commonly this is a bilateral disease; however, it may be focal and unilateral. Flasters, et al[5] cited fifteen cases of unilateral disease up to 1975, in which nephrectomy was curative. They also reported one case of exsanguinating hemorrhage requiring nephrectomy; no such other case had been reported up to 1975. Perusal of the literature revealed no reports of the same for 1976, 1977, or 1978.

The following is a case report of papillary necrosis, renal infarction, and threatened exsanguinating hemorrhage, seemingly not unlike the single case that Flaster reported in 1975.[5]

Case Report

This 86-year-old female was seen as an out-patient on the third of January 1977 with a tenosynovitis of the left hip, secondary to a degenerative arthritis. A complete blood count and urinalysis were within satisfactory limits. The hemoglobin was 12 gms. %, the white blood count was 12,000 and the neutrophile count was 78%. The lymphocyte count was 22%. The hema-combistix was normal. Microscopic examination of the urine revealed no red blood cells.

A ten day course of Sterazolidine® relieved her symptoms and the urinalysis remained normal on the 20th of January 1977. The patient voluntarily took acetaminophen 650 mg. daily until March 1977.

On the 11th of March 1977, the patient was again complaining of pain occasionally in the left lower quadrant and her hips were again painful. Physical examination was essentially normal for her age. There was no splenomegaly and there were no petechiae. The

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Fig. 1



Fig. 2



Fig. 3



Fig. 4

hema-combistix test was positive for blood and the microscopic urine contained multiple red blood cells. The hemoglobin was 13 gms. %. The white blood count was 7,800. The neutrophiles were 60%. The lymphocytes were over 40%. Serum glutamic pyruvic transaminase was 18. The blood urea nitrogen was 24. The blood sugar was 90.

On the 11th of April, the patient was without symptoms and was still taking acetominophen. She was asymptomatic. The urine still contained microscopically, red blood cells. The pelvic examination was normal except for a mild prolapse of the urethra. The patient was advised to take no drugs. A "Pap" smear of the cervix was normal.



Fig. 5



Fig. 6

On the third of May 1977, a cystoscopy was carried out which revealed a normal bladder and urethra. Microscopic studies of the urine revealed crenated red blood cells. Catherized urine yielded no growth.

On the 11th of May 1977, at another hospital, an intravenous pyelogram was interpreted as being within normal limits. In retrospect, however, one may note a filling defect of the upper calyx (See Fig. 1).

In July 1977, the patient was hospitalized in another hospital for tenosynovitis of the left hip. Her treatment consisted of Dolene.® Lumbo-sacral and pelvic films taken on August 25, 1977, revealed degenerative changes of the lower spine.

In September 1977, the patient's radiculitis had improved and she was without symptoms. The urine contained no white blood cells, red blood cells, or protein. The blood urea nitrogen was 24. The white blood count was 8,700. The neutrophils were 58% and the lymphocytes were 42%. The alkaline phosphatase was 9 Bodansky units. The blood sugar was 90 mgs. %.

On the 6th of December 1977, the patient had a sudden onset of painless hematuria. Eventually this was accompanied by severe left renal colic. At another hospital, an intravenous pyelogram demonstrated a normal right nephrogram but very little dye was excreted on the left (See Fig. 2).

The patient was transferred to the Seton Unit of the Mid-Maine Medical Center on the 8th of December 1977. On admission there was a mild elevation of the blood pressure. A temperature of 100° and mild costo-vertebral angle tenderness on the left were noted. There were no cardiac murmurs, no splenomegaly, or petechiae. No abnormal masses were demonstrated. The S.M.A. was normal. The urine was grossly bloody. The hemoglobin was 11.6 gms. %. The white blood count was 17,000. The hematacrit was 32%.

At cystoscopy on the 9th of December 1977, a cylindrical 2 cm. particle of debris, not unlike a sloughed papilla, was removed from the bladder. The histological report was amorphous debris. A few islands of transitional epithelium were attached to the periphery. There was no evidence of degenerating tubules or renal tissue in the specimen.

A catheter was inserted in the left ureter. After irrigation, dark bloody urine flowed from the catheter. Cultures yielded no growth. Fig. 3 demonstrates the retrograde pyelogram performed at this time.

The film revealed multiple radiolucencies in the renal pelvis and ureter. Mild dilation of the renal pelvis was demonstrated. There was marked parenchymal backflow with contrast material filling medullary pockets.

Bilateral renal arteriogram following the retrograde pyelogram, revealed excellent renal outline and arterial aborization on the right. The left renal arteriogram lacked terminal aborization with several "cut-offs" of the terminal branches of the renal artery along with poor renal outline. (See Fig. 4)

Ureteral catheter drainage was maintained according to the method of Jones and Macron.° The output from the left kidney increased from 200 c.c. on the first postoperative day to 1700 c.c. on the fourth postoperative day. Hematuria persisted from the left kidney until the third postoperative day. The patient was then asymptomatic.

On the 12th of December 1977, a left renal venogram revealed patency without evidence of thrombosis of the renal vein. (See Fig. 5).

When the patient was free of signs and symptoms of uropathy on the 13th of December 1977, a retrograde pyelogram via the previously placed ureteral catheter was accomplished. The mid and lower calyces were well defined on the left. There was a non-filling of the upper calyx with an irregular filling defect projecting into the pelvis at the origin of the major calyx. Medullary pocketing of the contrast media was absent (See Fig. 6).

There was a hemoglobin change from 12 gms. % on the 7th of December to 9 gms. % on the 12th of December 1977. The hematacrit dropped from 38 on the 7th of December 1977 to 28.3 on the 12th of December 1977. One unit of packed cells was given and the ureteral catheter was removed on the 15th of December 1977. The patient's course was one of progressive improvement.

Multiple blood cultures and urine cultures yielded no pathogens. There was no azotemia and a leukocytosis of 17,000 on admission returned to normal. An intravenous pyelogram on the 20th of December 1977 appeared normal except for a small cyst on the right. There was normal function on the left with minimal spasticity of the upper calyxceal area. There was still no medullary



Fig. 7



Fig. 8

pocketing of the dye (See Fig. 7).

The patient left the hospital without signs or symptoms on the 24th of December 1977. Throughout January 1978, the patient was without symptoms but microscopically red blood cells continued to be demonstrated in the urine. An intravenous pyelogram on the 27th of January 1978 revealed no significant change (See Fig. 8).

Readmission of the patient occurred on the 12th of February 1978. At this time, she had had painless intermittent gross hematuria since her intravenous pyelogram of the 27th of January 1978. Twenty-four hours before admission, severe left renal colic ensued. Physical examination was essentially the same except for tenderness in the left renal area. A hemoglobin drop from 13 gms. % of December 1977 to 8.5 gms. % in February 1978 was noted. The S.M.A. bleeding and clotting factors were normal. The EKG revealed non-descript S-T changes consistent with her age. A small area of atelectasis was noted on the chest film.

Because of the severe bleeding, a nephrectomy was carried out on the 14th of February 1978. Grossly the kidney revealed three (one cm.) small infarcted areas over the cortex. On bisection, gross necrosis was noted in the superior papillary area. Microscopically, focal areas of hemorrhagic infarction of the cortex and acute tubular necrosis was noted. The transitional epithelium appeared to be sloughed.

On the 24th of February 1978, ten days post-nephrectomy, the patient was discharged from the hospital. For eight months the patient has had no genito-urinary symptoms. She has had no gross or microscopic hematuria. She has been hospitalized at another hospital for non-descript chest pains.

Her blood pressure on the 11th of July 1978 was 164/80. The chest was clear to percussion and ausculation. The abdomen was without bruits, tenderness, or masses. The hemoglobin was 14 gms. %. The blood urea nitrogen was 20. Her urine was without albumin or red blood cells.

Summary

Papillary necrosis is reviewed. A case not unlike the sole reported case of threatened exsanguinating unilateral papillary necrosis by Flaster[5] is described. An apparent cure was obtained by nephrectomy.

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Nitrofurantoin

Richard Gleckman, M.D., Salvador Alvarez, M.D. and Dennis W. Joubert, B.S.

Abstract

Nitrofurantoin is a broad spectrum antimicrobial agent that has been available for clinical use for approximately 25 years. Its mechanism of action is not well understood, and the drug has the capability of inducing life-threatening events. Nitrofurantoin compares favorably with other standard agents for the therapy of acute and recurrent urinary tract infections in women due to susceptible organisms, and it is an effective chemoprophylactic agent for patients with recurrent urinary tract infections. The compound has no apparent adverse effects on the developing fetus and can be used in pregnant women. This is not sanctioned by the package insert, however. Nitrofurantoin should not be administered when the possibility of bacteremia exists, as the drug does not achieve therapeutic serum levels when administered orally. Nitrofurantoin is contraindicated for patients with renal insufficiency. The value of this compound for men with acute urinary tract infection, recurrent urinary tract infection, acute bacterial prostatitis or chronic bacterial prostatitis has not been established. There are no indications for prescribing parenteral nitrofurantoin.

Nitrofurantoin, a broad spectrum chemotherapeutic compound of the nitrofuran family, was introduced into clinical practice in 1953. It is currently prescribed for two indications: as definitive therapy of an established urinary tract infection and as a prophylactic agent for patients with recurrent urinary tract infections.

Mechanism of Action

The exact mechanism of action of nitrofurantoin is unknown. The drug may inhibit acetyl-coenzyme A, thus interfering with bacterial carbohydrate metabolism.[1-6] There is also evidence that nitrofurantoin disrupts the normal process of bacterial cell wall formation.[7] In contrast with the sulfonamides, the antimicrobial activity of nitrofurantoin is not impaired by the presence of pus.[8]

Antimicrobial Spectrum

Nitrofurantoin is a bactericidal compound, and susceptible organisms do not readily develop resistance during treatment.[9-12] There are conflicting data on the influence of pH on the therapeutic activity of nitrofurantoin.[10,13] One group of investigators reported that the chemotherapeutic activity was greatest at pH 5.4 and markedly reduced at pH 8.1.[10] However, this observation was not confirmed by others.[13]

In vitro drug susceptibility tests reveal a consistent pattern for those bacteria which cause most urinary tract infections.[9,10,14-41] The vast majority of *Escherichia coli, Citrobacter* species, group B streptococci, enterococci, *Staphylococcus aureus* and *Staphylococcus epidermidis* are susceptible to nitrofurantoin. Virtually all *Pseudomonas aeruginosa* and *Pseudomonas cepacia* are highly resistant. Most *Klebsiella pneumoniae* and *Enterobacter* species are susceptible. The susceptibilities of *Proteus* (mirabilis, morganii, vulgaris, rettgeri), *Providencia* species and *Serratia* species are controversial, with the percentage of susceptible strains varying markedly in different laboratories. This is partly explained by a lack of standardization, with microbiologists using different discs, inoculum and interpretations.[42]

The pattern of susceptibility of urinary pathogens to nitrofurantoin has persisted with only minor variation since the introduction of the drug.[43] Nitrofurantoin also demonstrates in vitro activity for *Salmonella* species, *Bacteroides* species and *Streptococcus pneumoniae*, which are very rare causes of urinary tract infections.[44-49] Most strains of *Acinetobacter*, an organism associated with nosocomial urinary tract infections, are resistant.[50]

Pharmacology

Nitrofurantoin is a weak acid with a pKa of 7.2. The compound is marketed as an oral suspension (25 mg/5 ml), tablets (50 and 100 mg), and parenteral liquid (180 mg/20 ml). The latter is virtually never used in medical practice.

Absorption

The oral suspension and tablets are well absorbed from the small intestine, as gastric absorption is negligible.[51] Absorption appears to occur in accordance with the "pH partition theory," which

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states that drugs undergo enhanced absorption when they exist in the unionized state at the site of absorption.

An oral dose of nitrofurantoin yields insignificant serum levels in patients with normal renal function.[52,53] Intramuscular administration of 180 mg of nitrofurantoin yields peak serum levels that average 3.3 μg/ml.[54] The plasma half-life is approximately 20 minutes.[55,56] Repeated oral dosing in patients with impaired renal function leads to accumulation of toxic concentrations of nitrofurantoin.[57-60]

A number of studies have compared the bioavailability of commercial nitrofurantoin preparations.[61-64] One investigator noted that 2 of 14 products tested resulted in an altered urinary excretion rate.[64] The urinary concentrations did not persist as long as with the other 12 preparations, even though the two faulty products fulfilled USP specifications for dissolution rate and disintegration time.

The relative bioavailability of microcrystal and macrocrystal nitrofurantoin has been evaluated.[65,66] The macrocrystal is more slowly absorbed and has a prolonged excretion time. The percentage of macrocrystalline drug excreted in the urine, as compared to microcrystal nitrofurantoin, is reduced by a small and clinically unimportant amount.

The bioavailability of nitrofurantoin is enhanced when the drug is taken with food.[67,68] The amount of drug absorbed and the duration of therapeutic urinary concentrations are significantly increased. Propantheline also enhances nitrofurantoin bioavailability, presumably by prolonging gastric retention and allowing more complete dissolution.[69]

Distribution and Excretion

Nitrofurantoin is excreted almost exclusively in the urine and bile.[51] Urinary excretion results from glomerular filtration, tubular secretion, and tubular reabsorption.[51,52] In an alkaline urine, renal clearance is enhanced as tubular reabsorption is diminished.[51] Approximately 40% of ingested drug is recovered intact in the urine.[55] Following oral administration of 100 mg four times a day, 57 to 185 mg may be recovered in the urine over a 24 hour period.[18]

Nitrofurantoin does not penetrate aqueous humor, cerebrospinal fluid, prostatic secretions, amniotic fluid or umbilical cord serum in therapeutic concentrations when administered parenterally to man or animals.[51,53] Oral administration to breast feeding mothers results in minimal drug concentrations in breast milk.[70-72]

Nitrofurantoin does not appear to exert any untoward effects on the fetus when administered to the pregnant female.[73]

Renal lymph concentrations of nitrofurantoin, a possible reflection of renal tissue concentrations, have been measured in animals, but not in man.[74,75]

Excretion in Patients with Impaired Renal Function

Nitrofurantoin has been studied extensively in patients with various degrees of renal insufficiency.[57-60,76,77] The excretion of the drug is directly related to creatinine clearance.[60] Patients with mild reduction of glomerular filtration fail to excrete nitrofurantoin in therapeutic concentrations, and thus the drug is contraindicated for the azotemic patient.[57-60,76,77] In the presence of severe uremia, nitrofurantoin serum concentrations are only modestly increased, not exceeding 6 μg/ml, however.[60] Presumably non-renal mechanisms of excretion dispose of the absorbed drug.

Interactions

It had been suggested that antacid therapy would increase the ionization of nitrofurantoin, resulting in decreased absorption,[78] but this has not been confirmed.[79]

Nitrofurantoin is a potent inhibitor of primary ADP-induced platelet aggregation in vitro.[80,81] The significance of this observation is not established.

Nitrofurantoin can alter a number of laboratory test results. There may be elevation of the urinary creatinine value, and the urine glucose determination using Benedict's reagent may yield a false-positive result.[82,83] Serum levels of glucose, bilirubin, alkaline phosphatase and blood urea nitrogen may be spuriously elevated.[82-84]

Miscellaneous

Patients should be warned that the color of the urine may be altered (brown) and that nitrofurantoin should be ingested with meals. The latter advice is based on the empirical observation that patients will probably tolerate the medication better (experience less nausea and vomiting), and there will be enhanced absorption.[85]

Adverse Reactions

Adverse reactions to nitrofurantoin are frequent. A survey of untoward events experienced by hospitalized patients revealed an incidence of 9.2%.[86] Adverse reactions have included gastrointestinal disturbances, skin eruptions, hematologic disorders, neurological defects, hepatotoxicity, pulmonary complications and miscellaneous abnormalities.

Gastrointestinal disturbances (anorexia, nausea, vomiting) are the most common side effects.[86-90] Nausea and vomiting usually develop during the first week of therapy, are experienced more often by women than men or children, and appear to be related to the daily drug dose and the patient's weight.[86] Efforts have been made to reduce the frequency of nausea and vomiting by altering the nitrofurantoin crystal size, thus modifying the absorption.[91] An initial study suggested that patients were able to tolerate the macrocrystalline form better than crystalline nitrofurantoin.[92] A subsequent double-blind comparison confirmed this finding.[93]

Skin eruptions, consisting of macular, maculopapular or urticarial lesions, are the second most common side effect of nitrofurantoin.[86,90,94,95] These were experienced by 1% of the hospitalized patients

who received nitrofurantoin.[96]

Hematologic Toxicity

Hemolytic anemia in patients with red blood cells deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD) is a well documented hematologic complication of nitrofurantoin therapy.[97] G6PD deficient erythrocytes have a reduced capacity to generate NADHP (reduced nicotinamide-adenine dinucleotide) and cannot cope with oxidant stress.[98] The NADHP is critical to the generation of reduced glutathione. Exposure to nitrofurantoin further compromises reduced erythrocyte glutathione generation by inhibiting erythrocyte glutathione reductase, the enzyme which converts oxidized glutathione to the reduced form.[99] Nitrofurantoin-induced hemolytic anemia has developed in children[100] and adults [94,101-109] and is not restricted to American black men.[109] Nitrofurantoin has also precipitated hemolytic anemia in patients who are deficient in other erythrocytic enzymes, namely enolase and glutathione-peroxidase.[110,111] Hemolysis has also been reported in a patient who had no known erythrocyte enzymatic deficiency.[112]

A few published reports have associated nitrofurantoin therapy with leukopenia,[8,113] megaloblastic anemia,[114,115] thrombocytopenia,[116] agranulocytosis[117-119] and aplastic anemia.[119,120] Some of these data are difficult to interpret, however.[121-123] One report described a 41% incidence of eosinophilia among patients who received nitrofurantoin.[124]

Neurotoxicity

A serious and frequent adverse reaction to nitrofurantoin is peripheral polyneuropathy.[125,126] This has also been attributed to other nitrofuran compounds, nitrofurazone and furaltadone.[127] Nitrofurantoin-induced polyneuritis has occurred in children[128,129] and adults[130-136] and usually develops in a setting of azotemia. Electromyographic abnormalities as well as symptomatic polyneuritis have also occurred in non-azotemic patients receiving nitrofurantoin.[137-140]

The onset of the polyneuropathy is usually insidious and symmetrical, occurring after days to years of either continuous or intermittent nitrofurantoin therapy.[141,142] The initial symptoms include paresthesias and dyesthesias, and arise more often in the lower than the upper extremities.[125] There is progression in a matter of days to include a number of sensory deficits, including impairment of pain, light touch and vibration. All symptoms and physical findings begin distally and spread centripetally. Weakness and muscle wasting ensue, and result in a flaccid paresis. The severity of symptoms is not related to the total amount of drug ingested.[126]

The polyneuritis may resolve completely, incompletely, or not at all. The amount of nitrofurantoin ingested is not related to the degree of recovery, and resolution of the polyneuropathy varies inversely with the severity of the muscle weakness.[126] Complete recovery usually occurs within weeks, although it may happen within days to months. Sensation returns faster than muscle strength.

Histopathological abnormalities in peripheral nerves have included demyelination, Wallerian degeneration, and fusiform swelling of axis cylinders.[130-132,141] Microscopic derangements of anterior horn cells have also been described.[143]

In addition to peripheral neuropathy, nitrofurantoin has been associated with reversible intracranial hypertension,[144,145] cerebellar dysfunction,[146] retrobulbar neuritis[147] and trigeminal neuralgia.[148]

Hepatotoxicity

Nitrofurantoin-induced hepatotoxicity is a rare event that is usually readily reversible with discontinuation of the medication.[99,149-152] However, persistent liver function abnormalities,[153-155] life- threatening hemorrhage, and death have been reported.[156-157] Hepatotoxicity is not dose-related, and jaundice is not invariable.[158] Some patients will experience fever, rash and arthralgia,[154-159] Eosinophilia, elevated serum transaminase or alkaline phosphatase values are not consistently noted.[154] Immunological abnormalities, including the development of antinuclear antibodies and antismooth muscle antibodies are detected in some patients.[151,152] Liver pathology has included intrahepatic cholestasis,[149,150,160] minimal cellular injury[161] and chronic active hepatitis.[151-153]

Pulmonary Toxicity

Nitrofurantoin-induced pulmonary reactions have developed in hundreds of patients. This untoward reaction has been arbitrarily classified into acute, subacute, and chronic forms.

The "classical" acute pulmonary reaction syndrome is characterized by the sudden onset of fever, chills, cough, myalgia and dyspnea (with or without cyanosis); rales at the lung bases; lower lobe infiltrates on chest x-ray (with or without effusion); rapid resolution of clinical and radiological abnormalities following discontinuation of the medication; an elevated sedimentation rate; delayed onset of peripheral blood eosinophilia; and recurrence of similar clinical manifestations, with a shortened incubation period, on subsequent exposure.[162-195] This reaction develops within hours to weeks of the ingestion of the drug and can be accompanied by headache, rash, generalized pruritis, chest discomfort, sputum production and shock. The syndrome has been mistaken for congestive heart failure,[162-169] pulmonary embolism,[170-173] bacterial pneumonia,[174,175] an asthmatic attack,[176] anaphylaxis,[177,178] myocardial infarction[177,179,180] or pericarditis,[179] influenza[180] and Loffler's syndrome.[181] On rare occasions the chest x-ray demonstrates no abnormalities.[180,182] Pulmonary function studies demonstrate a restrictive lung pattern, ventilation/perfusion abnormalities and arterial-venous shunting, accompanied by hypocapnia and hypoxemia.[183] Lung biopsy reveals alveolar exudation, interstitial inflammation and vasculitis.[179] The value of

steroid therapy in accelerating recovery is unproven. The reaction almost always resolves completely, although at least one fatality has been reported.[184] The acute pulmonary nitrofurantoin reaction may be a sensitivity phenomenon mediated via specific cellular reactivity to the drug and not by an antibody response.[185-187]

Subacute pulmonary reactions from nitrofurantoin usually develop after one month of drug exposure and are characterized by persistent and progressive cough, dyspnea, orthopnea and fever.[179,196] Radiographically there is interstitial pneumonitis. There may be an associated lupus-like syndrome consisting of arthralgia, pleural effusions, peripheral lymphadenopathy, impaired liver function, elevated sedimentation rate, polyclonal hypergammaglobulinemia, positive latex-agglutination test, antinuclear antibodies and antibodies to thyroid, glomeruli and smooth muscle.[197,198] Discontinuation of nitrofurantoin therapy is followed by complete resolution of all abnormalities.

The chronic nitrofurantoin pulmonary reaction is associated with the insidious development of nonproductive cough and dyspnea.[173,179,199-210] Physical examination reveals rales, but fever is not a consistent finding. The sedimentation rate is usually elevated, and there may be abnormalities of liver function tests.[199] Peripheral blood eosinophilia is absent. Pulmonary function studies demonstrate a restrictive ventilatory pattern with impairment of carbon dioxide diffusing capacity.[200] Histologically there is nonspecific diffuse interstitial pneumonitis and fibrosis.[200,201] Desquamative interstitial pneumonitis has also followed prolonged therapy with nitrofurantoin.[202,203] The chronic nitrofurantoin pulmonary reaction develops after six months of drug treatment[199] and has occurred in children.[203] Usually, but not always, regression of the syndrome follows discontinuation of nitrofurantoin therapy.[204] Treatment with a steroid may improve symptoms, but there is no firm evidence that pulmonary function or radiographs are improved.[199,205] Irreversible pulmonary fibrosis culminating in respiratory failure and death has resulted from long-term treatment with nitrofurantoin.[173,199,207]

Miscellaneous

Miscellaneous untoward events ascribed to nitrofurantoin have included angioneurotic edema,[211] alopecia,[212] fever[213] and crystalluria.[214]

Therapeutic Use

Nitrofurantoin was introduced into clinical practice in 1953. During the last ten years, however, understanding of what constitutes a therapeutic "response" has progressed considerably. Many early therapeutic trials do not meet current standards of clinical trial designs, and cannot be critically interpreted. This article reviews only more recent studies that carefully define the patient population, pretherapy organism, "in vitro" drug susceptibility, dose and duration of therapy, concomitant influencing factors (structural abnormalities, calculi, neurogenic bladder, etc.) and the pattern of response (cure, reinfection, relapse). In addition, the cited publication had to describe the laboratory procedures and include quantitative microbiology.

The conventional dosage of nitrofurantoin for an established urinary tract infection is 50 or 100 mg four times a day. One study suggests that these doses produce comparable clinical and bacteriological response rates.[17]

Treatment of Acute Symptomatic Urinary Tract Infection

Adults. Cure rates in non-hospital *E. coli* urinary tract infections among adult women who have received nitrofurantoin are approximately 75%[215] The therapeutic response correlates directly with the tissue source of the infection, since women with acute cystitis are more frequently cured than are women with pyelonephritis.[216] Thus, nitrofurantoin constitutes a very effective therapy for acute symptomatic urinary tract infections in women caused by *E. coli*[10,88] and compares favorably with ampicillin.[215] The therapeutic response is considerably worse when *Proteus mirabilis* is the etiological agent.[215]

Acute symptomatic urinary tract infections in men are often associated with structural abnormalities and accompanied by bacteremia. Since oral nitrofurantoin does not achieve therapeutic concentrations in serum, it should not be administered in this situation.

Children. Nitrofurantoin is very effective therapy of acute symptomatic urinary tract infections caused by *E. coli* in children.[217,218] The initial bacteriological response exceeds 90%. Ampicillin, sulfonamide, and nitrofurantoin appear equally effective.[217,218] For established infection an appropriate amount is 5 to 10 mg/kg daily, divided into four equal doses.

Recurrent Urinary Tract Infections

Adults. Nitrofurantoin treatment produced an 80 to 100% immediate cure rate of urinary tract infections in women without obstructive uropathy who had asymptomatic bacteriuria and/or documented recurrent urinary tract infections caused by *E. coli*.[90,219-223] The results were not improved by extending the duration of therapy from 2 to 6 weeks.[220] The majority of "failures" are reinfections, defined as recurrent infection caused by an organism different from that producing the original infection. Reinfection probably reflects impaired host defenses rather than drug failure.[224] Therapeutic efficacy was not enhanced when alternative standard agents were prescribed for these women.[90,219-221]

Patients with what was formerly termed "chronic urinary tract infections" (currently termed "recurrent" infections), due to *E. coli* and *Enterobacter* species, experienced immediate therapeutic response from nitrofurantoin, but significant bacteriuria recurred when chemotherapy was discontinued.[94]

Limited data suggest that nitrofurantoin is not very effective for recurrent urinary tract infections in men. This is explained by the fact that most recurrent

urinary tract infections in men are caused by chronic bacterial prostatitis and infection stones.[224]

Children. Approximately 90% of the nitorfurantoin treatment courses in children with recurrent urinary tract infections resulted in immediate bacteriological cure.[225] However, virtually all these patients later developed another recurrence. Nitrofurantoin is as effective as a sulfonamide or a tetracycline for the therapy of recurrent urinary tract infections in children.[225]

Prophylaxis of Recurrent Urinary Tract Infections

Adults. Recurrent urinary tract infections in women have been prevented by a single dose of nitrofurantoin administered after intercourse[226] and by continuous single nightly doses taken over a prolonged time.[90,221,227-231] The data demonstrate that nitrofurantoin is a more effective prophylactic agent than placebo[221,227] and compares well with other chemotherapeutic agents.[90,221,228-231] Recurrent infections occurring during therapy are usually caused by nitrofurantoin susceptible organisms.[230] Since nitrofurantoin does not produce resistance in the fecal flora, this probably ensures reinfection with drug susceptible bacteria.[232] When continuous nitrofurantoin prophylaxis is discontinued, however, the recurrence rate over the next six months is considerable.[90,93,229] This is not unique to nitrofurantoin, but characteristic of women with recurrent urinary tract infections.[233]

Continuous prophylactic treatment with nitrofurantoin has resulted in a decreased incidence of recurrences in men with chronic urinary tract infections.[234]

For adult women, a single nightly dose of 50 mg of nitrofurantoin is effective prophylaxis for recurrent urinary tract infections.[221,227-229] For adult men a dose of 50 mg of nitrofurantoin administered four times a day is effective prophylaxis,[234] but a lower dose might be equally effective.

Children. Nitrofurantoin prophylaxis convincingly decreased the incidence of recurrent urinary tract infections in children having no evidence of anatomic urinary tract abnormalities.[235,236] The incidence of recurrences was not diminished when prophylactic nitrofurantoin was administered to children with meningomyelocele.[237] A single evening dose of 1 to 2 mg/kg is an effective amount of nitrofurantoin for the prevention of recurrent urinary tract infections in children.

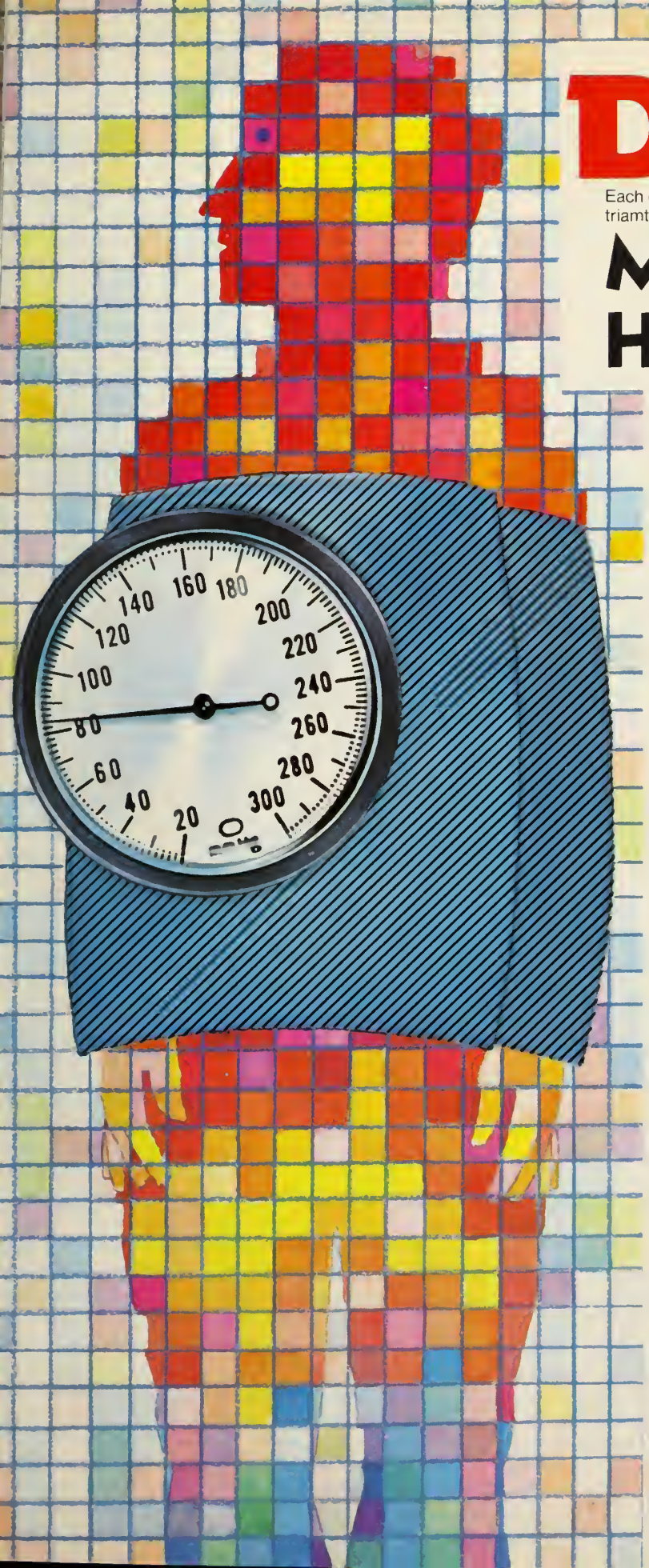
Therapeutic Indications

The frequency and potential severity of reactions attributed to nitrofurantoin, combined with its inability to achieve therapeutic blood concentrations, relegate this compound to a position of secondary importance. Nitrofurantoin should not be administered to patients with acute bacterial pyelonephritis (as this disease can be accompanied by bacteremia) or to men with recurrent urinary tract infections, and it should not be an agent of first choice for patients with acute bacterial cystitis or recurrent urinary tract infections. Indications for nitrofurantoin could include the following: treatment of the penicillin-sensitive or cephalosporin-sensitive patient who has acute symptomatic bacterial cystitis or a recurrent urinary tract infection unassociated with bacteremia and caused by a nitrofurantoin-susceptible organism; chronic prophylactic treatment for the child or adult who experiences multiple disabling symptomatic exacerbations of recurrent urinary tract infections; and chronic prophylactic treatment for the child with reflux nephropathy who experiences recurrent asymptomatic urinary tract infections.

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Dyazide

Each capsule contains 50 mg. of Dyrenium* (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Makes Sense in Hypertension*

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

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This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964

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Brief Summary
INDICATIONS
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IT SHOULD BE NOTED AT THIS POINT IN TIME THAT THERE IS A LACK OF CONCURRENCE AS TO THE VALUE OF ANTICHOLINERGICS/ANTISPASMODICS IN THE TREATMENT OF GASTRIC ULCER. IT HAS NOT BEEN SHOWN CONCLUSIVELY WHETHER ANTICHOLINERGIC/ANTISPASMODIC DRUGS AID IN THE HEALING OF A PEPTIC ULCER, DECREASE THE RATE OF RECURRENCES, OR PREVENT COMPLICATION

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the following indications as "probably" effective.

May also be useful in the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis, acute enterocolitis, and functional gastrointestinal disorders); and in neurogenic bowel disturbances (including the splenic flexure syndrome and neurogenic colon).

THESE FUNCTIONAL DISORDERS ARE OFTEN RELIEVED BY VARYING COMBINATIONS OF SEDATIVE, REASSURANCE, PHYSICIAN INTEREST, AMELIORATION OF ENVIRONMENTAL FACTORS

For use in the treatment of infant colic (syrup).

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS. Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis. WARNINGS. In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: autonomic neuropathy; hepatic or renal disease; ulcerative colitis—Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon; hyperthyroidism; coronary heart disease; congestive heart failure; cardiac arrhythmias; and hypertension; hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

It should be noted that the use of anticholinergic/antispasmodic drugs in the treatment of gastric ulcer may produce a delay in gastric emptying time and may complicate such therapy (antral stasis). Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia, urinary hesitancy and retention, blurred vision and tachycardia; palpitations; mydriasis, cycloplegia, increased ocular tension; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION. Dosage must be adjusted to individual patient's needs.

Usual Dosage. Bentyl 10 mg. capsule and syrup: *Adults*: 1 or 2 capsules or teaspoonfuls syrup three or four times daily. *Children*: 1 capsule or teaspoonful syrup three or four times daily. *Infants*: ½ teaspoonful syrup three or four times daily. (May be diluted with equal volume of water.) Bentyl 20 mg.: *Adults*: 1 tablet three or four times daily. Bentyl Injection: *Adults*: 2 ml. (20 mg.) every four to six hours intramuscularly only. NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE. The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing. CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

Product Information as of October, 1976

Merrell

MERRELL NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215, U.S.A.

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County Society Notes

Piscataquis

The Fall meeting of the Piscataquis County Medical Society was called to order at 9:15 p.m. on September 20, 1978 at Dr. Stitham's camp on Sebec Lake. Members present were Drs. Alley, Berry, Dahl, Garcia-Rey, Lightbody, Parker, Rodriquez, Stitham and Stone.

Under old business, Dr. Lightbody discussed the pending move of Maine Medical Association offices to Augusta, and the progress of the Medical Association's malpractice insurance company. Dr. Stone has recently been appointed to a PSRO committee on implementing the surgical opinions program in rural areas. Difficulties of getting a second surgeon's opinion in rural areas were discussed. Increasing difficulty in relationship of organized medicine at the Maine Blue Shield was discussed.

Dr. Stitham brought up the current problem of how to include any physicians who are not members of the Maine Medical Association in the activities of the county society. It was pointed out that a majority of the physicians in the area are not members of the County Society because they are Osteopathic Physicians, live and work just across the county line or object to being coerced into joining the Maine Medical Association. It was decided that the Fall meeting would be the annual meeting of the County Society and would be restricted to members only. All the official business and election of officers would take place at this meeting. Three other meetings would be held during the year which would combine the social, scientific and limited business session and all area physicians would be invited to these meetings.

Treasurer's report reveals $718.00 in the treasury. We discussed what to do with this surplus. It was decided that the costs of the next meeting at Squaw Mountain in September would be paid for out of this surplus.

We elected the following officers for 1979:
President, Dr. James W. Berry, Dover-Foxcroft
Vice-President, Dr. Linus J. Stitham, Dover-Foxcroft
Secretary-Treasurer, Dr. Howard G. Parker, Dover-Foxcroft
The meeting was adjourned at 10:30 p.m.

JAMES W. BERRY, M.D., *Secretary*

Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held on October 17, 1978 at The Ledges in Wiscasset, with nineteen members and guests present.

The Secretary gave a synopsis of the minutes of the September meeting and of a meeting he attended that same evening in Waterville at which the Dept. of Human Services discussed the formation of an advisory committee for Medicaid fee schedules.

Dr. Richard Evans discussed the offer of the Department of Psychiatry of the Maine Medical Center to set up meetings in county societies for continuing education in psychiatry for primary care physicians.

Mr. Frank Faherty of Blue Cross and Blue Shield of Maine was introduced as primary spokesman, with Messrs. Tim Joy and George Hansen, for BC/BS. They presented structure and policies of Blue Shield and discussed topics introduced by society members.

GEORGE W. BOSTWOCK, M.D., *Secretary*

News, Notes and Announcements

State of Maine
Department of Human Services
Division of Child Health Clinic Schedule—1979

By Appointment Only

Orthopedic Clinics

Bangor—St. Joseph Hospital
9:00 a.m.: Mar. 22, Apr. 26, May 24, June 28, July 19, Aug. 23, Sept. 27, Oct. 25, Nov. 15, Dec. 20
Fort Kent—Northern Maine Medical Center
9:00 a.m.: Mar. 13, May 15, July 10, Sept. 11, Nov. 6
Houlton—Houlton Regional Hospital
10:00 a.m.: Mar. 12, May 14, July 9, Sept. 10, Nov. 5
Presque Isle—A.R. Gould Memorial Hospital
9:00 a.m.: Mar. 14, May 16, July 11, Sept. 12, Nov. 7
Waterville—Mid-Maine Medical Center (Seton Unit)
Time scheduled by hospital: Mar. 5, Apr. 2, May 7, June 4, Sept. 10, Oct. 1, Nov. 5, Dec. 3

Cleft Palate Clinic

Portland—Maine Medical Center
9:00 a.m.: May 21, June 18, Sept. 17, Oct. 15, Nov. 19

Cardiac Clinics

Bangor—St. Joseph Hospital
9:00 a.m.: Mar. 9, Apr. 13, May 11, June 8, July 13, Aug. 10, Sept. 14, Oct. 12, Nov. 9, Dec. 14
Portland—Maine Medical Center
9:00 a.m.: Mar. 2, 9, 16, 23, 30, Apr. 6, 13, 20, 27, May 4, 11, 18, 25, June 1, 8, 15, 22, 29, July 6, 13, 20, 27, Aug. 3, 10, 17, 24, 31, Sept. 7, 14, 21, 28, Oct. 5, 12, 19, 26, Nov. 2, 9, 16, 30, Dec. 7, 14, 21, 28

Children's Development Clinic

Lewiston—Central Maine Medical Center
8:30 a.m.: Mar. 12, Apr. 9, May 14, June 11, July 9, Aug. 13, Sept. 10, Nov. 26, Dec. 10

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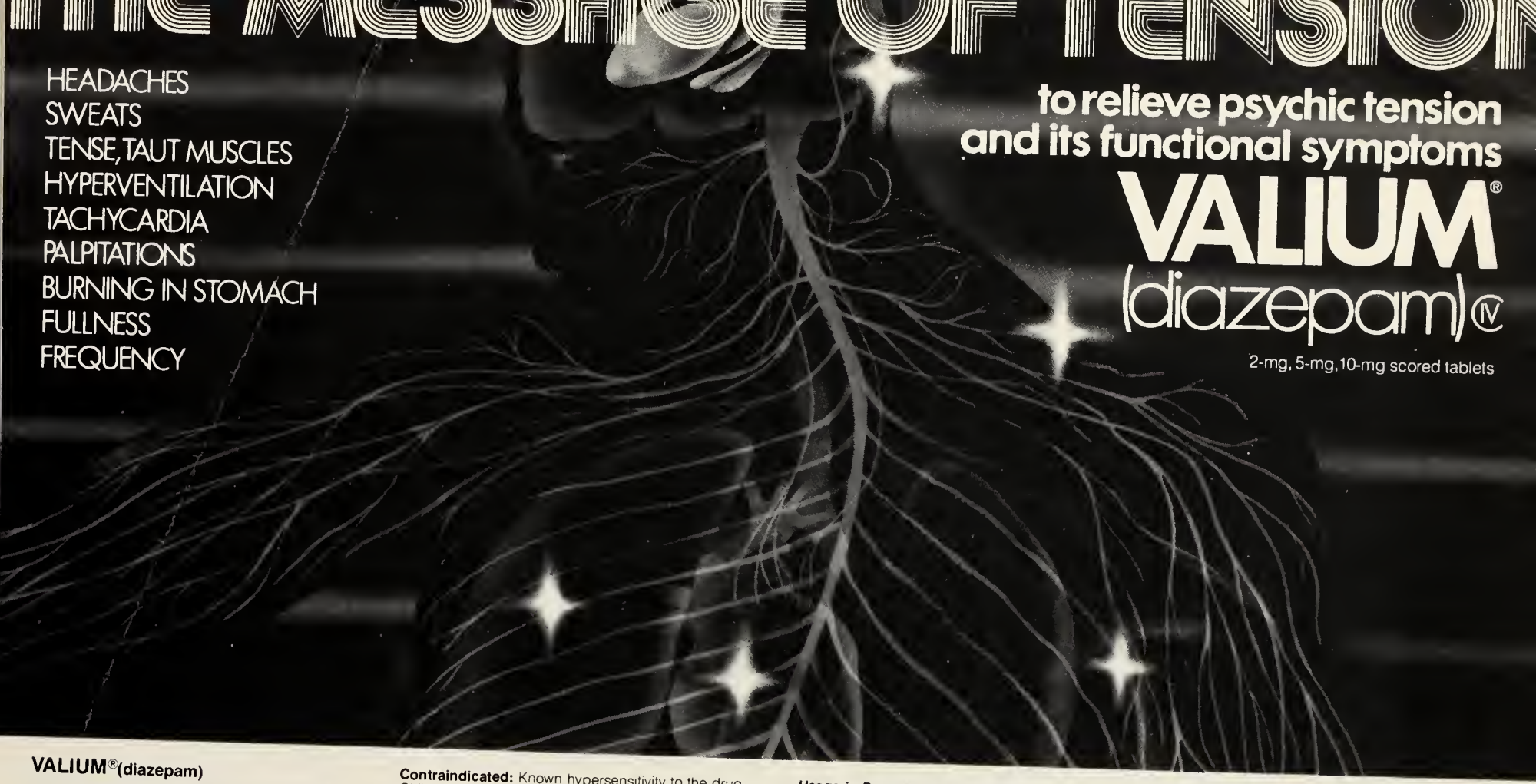
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Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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Changing Indications for C-Section

K. C. Leong, M.D., F.A.C.O.G.*

"The aims of prenatal investigation should not be to reduce fetal mortality to zero, but rather to assure the birth of an individual capable of functioning in society in a responsible and hopefully contributing manner."

Abstract

A review of the historical and current changing indications for C S, with drawbacks, is presented.

Our experience at CMMC parallels the nationwide trend.

Cesarian section is an old and dramatic surgical operation. The earliest records of its origin are traced to the reign of Numa Pompilius (715-672 B.C.), a legendary king of Rome, who decreed that the child be excised from the womb of any woman who died late in pregnancy. Known initially as the "lex regia" (royal law), the requirement for postmortum section continued under the rule of the Caesars, when it acquired the name "lex caesarea." The name of the operation is derived from the verb "caedere (to cut)." The purpose of the Roman Law was twofold; namely, to salvage a living fetus should the mother die undelivered or, under those tragic circumstances, to provide the child a separate burial. The preservation of the life of a viable fetus after death of the mother is still regarded as one of the indications for the operation. As might be expected, the fetal mortality is quite high, for the operation is performed after the mother has expired but when the fetal heart tones are believed to be still present. A careful follow-up is needed of the children so delivered; the risk of irreparable damage to the central nervous system from intrauterine hypoxia obviously is substantial.

No valid basis can be found for the widely held belief that Julius Caesar, born about 100 B.C., was delivered by abdominal section and that the operation was named for him; indeed, this myth is controverted by all available evidence. Then, the operation was done on the dead or dying, and for many centuries thereafter was uniformly fatal when attempted on the living woman. Yet Caesar's mother survived his birth by many years, as proved by his letters written to her while engaged in his foreign wars.

The first half of the nineteenth century saw a little improvement in the operation's record; in 1867, Myer reported a mortality of 54% among 1605 cases collected from the literature. In Paris, not one mother survived a Cesarian section during the 90-year period from 1787 to 1876; in Great Britain, the maternal mortality was recorded as 85%. By 1878, the operation had been carried out only 80 times in the United States, with a maternal mortality of 52.5%. Harris, who reviewed the American cases in 1878, noted that the chances for success seemed greater when the operation was performed remote from the centers of civilization. Five recoveries occurred among 9 rural patients who had operated upon themselves, in desperation, one having been gored by a bull. While in New York City during the same period, only 1 of 11 survived who had been operated upon by physicians.

Up until late in the 19th century it was vigorously debated whether Cesarian section (C S) was ever justified as opposed to a destructive operation, that is, craniotomy and embryotomy, when pelvic contracture precluded safe vaginal delivery and the fetus was still alive.

So far as records reveal, the first successful Cesarian section (C S) in the U.S. was performed in 1794 by Dr. Jesse Bennett upon his own wife in the backwoods country of Virginia. Following a consultation, after 3 days of labor and an unsuccessful attempt at pelvic delivery by forceps in the presence of a contracted pelvis, it was decided that two courses were open: C S or craniotomy. The decision was influenced in no small measure by the patient, who, thinking that she would die anyway, insisted that the child be saved if possible. Even though it was decided

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to perform a Cesarian operation, the consultant, Dr. Alexander Humphreys, refused to do the procedure, but did consent to assist Dr. Bennett. The mother survived and lived another 25 years, while the baby girl, unharmed, lived to the impressive age of 77 years. The records are authentic, although Dr. Bennett refused to report the case, for he believed that his critics would question his veracity and asserted that "no doctor with any feelings of delicacy would report an operation he had done on his own wife."

Indications for C-Section (C S)

Indications for C S are both absolute and relative. Any condition which makes delivery per vaginam impossible is an absolute indication for abdominal sections. Among these are extreme degrees of pelvic contraction and neoplasms blocking the passage. With a relative indication vaginal birth is possible, but the conditions are such that C S is safer for the mother, the child, or both. In the last few years, for various reasons, relative indications for C-Sections have increased in frequency.

Pelvic Contraction and Mechanical Dystocia

1.) Fetopelvic Disproportion: This includes the contracted pelvis, the oversized fetus, or a relative disparity between the size of the fetus and that of the pelvis. Contributing to the problem of disproportion is the shape of the pelvis, the presentation of the fetus and its ability to mold and engage, the dilatability of the cervix and the effectiveness of the uterine contractions.

The number of C-Sections for FPD (fetopelvic disproportion) has increased over the years. One study reported that 49% of primary C-Sections were performed for FPD. There are no data to support the concept that the pelves of females are becoming smaller or that babies are getting larger. Consequently, the concept of FPD in the mind of the obstetrician must have changed. Indeed, the term "failure to progress" has become an indication for C S in some institutions, and correctly indicates the reluctance of the obstetrician, in the interest of the fetus, to perform a mid-forceps delivery after an arrested labor. Some of the patients who have been sectioned for "failure to progress" have normal measurements by clinical and x-ray pelvimetry, have average size babies, and have had their contractions augmented by oxytocin.

In Friedman's series, perinatal mortality rates were 2 per 1000 after spontaneous delivery with normal labor, 11 per 1000 associated with mid-forceps deliveries following normal labors and 29 per 1000 followed prolonged labor terminated by mid-forceps delivery. Clearly, Friedman's study emphasizes the advantage of C S in this circumstance.

2.) Neoplasms: Neoplasms which block the pelvis make normal delivery impossible. Invasive cervical malignancy diagnosed in the last trimester of pregnancy is treated by C S, followed by radiation therapy, radical surgery, or both. The exact pro-

Continued on Page 93

Tenuate®
(diethylpropion hydrochloride NF)

Tenuate Dospan®
(diethylpropion hydrochloride NF) controlled-release

AVAILABLE ONLY ON PRESCRIPTION
Brief Summary
INDICATION: Tenuate and Tenuate Dospan are indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use such as those described below.
CONTRAINDICATIONS: Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result).
WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. *Drug Dependence*: Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy*: Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children*: Tenuate is not recommended for use in children under 12 years of age.
PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.
ADVERSE REACTIONS: *Cardiovascular*: Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System*: Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache, rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal*: Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic*: Urticaria, rash, ecchymosis, erythema. *Endocrine*: Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System*: Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous*: A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.
DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride): One 25 mg tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg tablet daily, swallowed whole, in midmorning. Tenuate is not recommended for use in children under 12 years of age.
OVERDOSAGE: Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phentolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product Information as of April, 1976
MERRELL-NATIONAL LABORATORIES Inc
Cayey, Puerto Rico 00633
Direct Medical Inquiries to
MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc
Cincinnati, Ohio 45215, U.S.A.
Licensor of Merrell®

References: 1. Citations available on request—Medical Research Department, MERRELL RESEARCH CENTER, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M.T., O'Dillon, R.H., and Leyland, H.M.: A Comprehensive Review of Diethylpropion Hydrochloride. International Symposium on Central Mechanisms of Anorectic Drugs, Florence, Italy, Jan. 20-21, 1977.

Merrell

8-3921 (Y587A)

Whether overweight is a complicating factor... or just uncomplicated overweight.

Tenuate® Dospan® ℂ℣
(diethylpropion hydrochloride NF)
75 mg. controlled-release tablets



A useful short-term adjunct in an indicated weight loss program.

Overweight patients in certain diagnostic categories often require strict obesity control. Diethylpropion hydrochloride has been reported useful in obese patients with hypertension, symptomatic cardiovascular disease, or diabetes. While it is not suggested that Tenuate in any way reduces these complications in the overweight, it may have a useful place as a short-term adjunct in a prescribed dietary regimen. (Tenuate should not be administered to patients with severe hypertension; see additional Warnings and Precautions on the opposite page.)

In uncomplicated obesity.

Many patients, on the other hand, present with excess fat but no disease. While this condition is often termed uncomplicated obesity, complications of both a social and a psychologic nature may be distressingly real for the patients. In these cases, a short-term regimen of Tenuate can help reinforce your dietary counsel during the important early weeks of an indicated weight loss program.

Clinical effectiveness.

The anorexic effectiveness of diethylpropion hydrochloride is well documented. No less than 16 separate double-blind, placebo-controlled studies attest to its usefulness in daily practice.[1] And the unique chemistry of Tenuate provides "...anorexic potency with minimal overt central nervous system or cardiovascular stimulation."[2] Compared with the amphetamines, diethylpropion has minimal potential for abuse.

Tenuate—it makes sense. And it's responsible medicine.

Merrell

For prescribing information see opposite page.











The evidence of experience

Since October 1974 when Motrin® (ibuprofen) was introduced in the United States, it has been used by more than 6,000,000 patients with rheumatoid arthritis* or osteoarthritis. Rarely has an ethical pharmaceutical product been prescribed for so many patients in so short a time. In addition, more than 450 studies presenting new data related to Motrin have been published.

The 6,000,000 patients already treated with Motrin is an objective measure of physicians' confidence in the ability of Motrin to relieve the pain and inflammation associated with rheumatoid arthritis and osteoarthritis.

So it is not surprising that in this short period Motrin has become the most frequently prescribed alternative to aspirin. Motrin relieves joint pain and inflammation as effectively as indomethacin or aspirin, but causes significantly fewer CNS and milder GI reactions. However, gastrointestinal bleeding, sometimes severe, has been associated with Motrin, aspirin, indomethacin, and other nonsteroidal antiarthritic agents.

*The safety and effectiveness of Motrin have not been established in patients with Functional Class IV rheumatoid arthritis (incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care).

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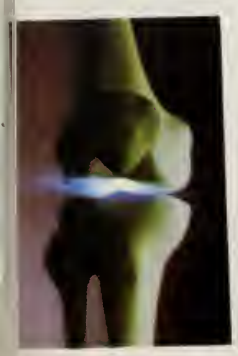












Motrin 400 mg TABLETS
ibuprofen, Upjohn

The confidence that comes from experience—one more reason to prescribe Motrin.

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

1685

The confidence that comes from experience—
one more reason to prescribe

Motrin 400 mg TABLETS
ibuprofen, Upjohn

Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin* used concomitantly may decrease Motrin blood levels. *Coumarin*: Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin (ibuprofen) is gastrointestinal (4% to 16%). This includes nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness*, headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

Incidence: Unmarked 1% to 3%; *3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Suggested dosage is 300 or 400 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day.

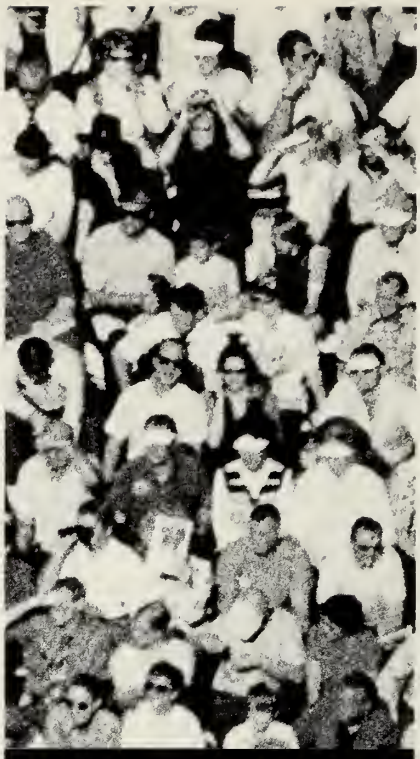
How Supplied

Motrin Tablets, 300 mg (white)	
Bottles of 60	NDC 0009-0733-01
Bottles of 500	NDC 0009-0733-02
Motrin Tablets, 400 mg (orange)	
Bottles of 60	NDC 0009-0750-01
Bottles of 500	NDC 0009-0750-02
Unit-dose package of 100	NDC 0009-0750-06
Unit of Use bottles of 120	NDC 0009-0750-26

Caution: Federal law prohibits dispensing without prescription.

NIM-3

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001



ALDOMET® (METHYLDOPA | MSD)

TABLETS: 500 mg, 250 mg, and 125 mg

MSD MERCK SHARP & DOHME

cedure varies in the different localities.

3.) Uterine Dysfunctions: Includes incoordinate uterine action, inertia, constriction rings, and inability of the cervix to dilate. Labor is prolonged and may cease altogether. These conditions are often associated with disproportion and malpresentation.

4.) Malposition and Malpresentation: Malposition and malpresentation may make C S necessary where a baby in normal position could be born vaginally. When the fetus is large and the pelvic architecture faulty, or when labor and progress are unsatisfactory, abdominal delivery is best. Impacted transverse lies are, in most cases, better treated by C S than by version and extraction.

The role of external version in modern obstetrics is controversial. However, if it is attempted, it appears that the use of ultrasound is helpful in avoiding complications by confirming the presentation, excluding multiple pregnancies and localizing the placenta. Perhaps indirect electronic monitoring of the fetal heart should also be done for a period of time after the procedure to rule out cord accidents.

Any discussion concerning management of breech presentation must consider the higher incidence of breech presentation in low birth weight infants, and the increased perinatal mortality and morbidity associated with vaginal delivery. Perinatal mortality is four times higher and morbidity 12 times greater when the breech is presenting. LBW babies are especially at risk of injury since in the premature, the head circumference exceeds that of the shoulders, and the head may be trapped behind a cervix sufficiently dilated to allow shoulder delivery, but not delivery of the head.

Subtle injuries in breech infants are frequent. A 9-year follow-up study of breech-delivered infants in the U.S. revealed that 24.5% had already repeated one or more grades, 31.9% were below "normal" in arithmetic achievement, and in 19.1%, remedial measures had been advised. Among infants delivered spontaneously or with low forceps the rates were 8.3, 15.2, and 7.7% respectively.

Because of different interpretations and conditions, practices vary throughout the world. Perinatal mortality rates remain high, especially in premature infants, among physicians who continue to deliver breech-presenting infants vaginally unless there are clinical indications for C S or who believe that the head may not be delivered without trauma. At many centers, breech-presenting infants are delivered by C S unless vaginal delivery is imminent, the fetus is dead or affected with a severe congenital abnormality, or there are maternal contraindications to C S. Maternal morbidity rates may be high with this approach. On the other hand, at some centers, vaginal delivery with continuous monitoring is planned except in certain circumstances such as the presence of a large fetus, abnormality or smallness of the pelvis suspected from physical or x-ray examination; anticipation of prolonged labor; dysfunctional labor; uterine abnormality; suspected compromise of the fetus; growth retardation; postmaturity, diabetes, preeclampsia, elderly prigravida or a history of infertility. If unfavorable changes occur during labor, C S is performed. With this approach, morbidity can be further reduced, especially among premature infants. It is hoped that adequately controlled studies among this latter group of patients, in whom all appears to be ideal for vaginal delivery, will define the best means of delivery or the fetal and maternal risks with each method of delivery.

5.) Soft Tissue Dystocia: May prevent or make difficult normal birth. This includes such conditions as scars in the genital tract, cervical rigidity from injury or surgery, and atresia or stenosis of the vagina. Forceful vaginal delivery results in large lacerations and hemorrhage.

Previous Uterine Surgery

1.) Previous C S: There are two schools of thought on the question of repeat C-Sections. One view is that once a Cesarian procedure has been performed, all subsequent pregnancies must be terminated by C S. It is felt that the danger of uterine rupture through the site of the previous incision is too great. The other school holds that, provided the first section was done for reasons other than disproportion and provided that the pelvis is adequate, the fetus is not excessively large, the presentation and position are normal and the cervix is favorable, a trial of labor should be allowed, with probable vaginal delivery. The patient must be under constant observation, cross-matched blood must be at hand, and the operating room must be ready for immediate surgery should the uterus rupture or threaten to do so. The danger of uterine rupture is less if the previous incision was in the lower segment.

Since the operation has been used for conditions other than FPD, the proper method of delivery to be used after a previous abdominal hysterotomy continues to be debated. In view of the improvement of C S mortality, the question of vaginal delivery after an antecedent abdominal hysterotomy has become even more controversial. When the conditions that impelled the previous C S are permanent or recurring, the decision is obvious. If the indication for the initial abdominal delivery was temporary and the conditions in the current pregnancy appear favorable for pelvic delivery, the choice of attempting pelvic delivery rather than performing a repeat C S becomes a matter of clinical judgement.

The facts to be considered in determining the method of delivery to be employed after previous C S include the type of section that was performed and whether the postoperative course was febrile, indicative presumably of primary healing of the uterine scar; the presentation of the fetus; the station of the presenting part; and the status of the cervix and the membranes at the onset of labor. Finally, the presence of pain and tenderness about the region of the previous uterine incision is generally held to reflect the possibility of impending or beginning rupture of the uterine wound.

2.) Extensive Myomectomy: C S indicated only if

the operation was extensive, the myometrium disorganized, and the incision extended into the endometrial cavity.

3.) Cervical Suture or Repair of an Incompetent Os: In the event that the surgical operation for incompetent cervix fails and signs of imminent abortion develop, it is urgent that the suture be released at once, since failure to do so promptly may result in grave sequelae. In successful cases from the McDonald procedure, the suture must be removed at the thirty-eighth or thirty-ninth week to allow labor to progress. After the Shirodkar operation, the suture may be left in place and a C S performed near term (a plan designed to prevent the necessity of repeating the procedure in subsequent pregnancies), or it may be released and vaginal delivery permitted, according to circumstances.

Hemorrhage

1.) Placenta Previa: C S for central and lateral placenta previa has reduced fetal and maternal mortality. The decision can be made by:

—Ultrasonography
—Placentography
—Vaginal examination in the operating room using a double set up.

2.) Abruptio Placenta: If occurring before or during early labor, may be treated by rupture of the membranes and oxytocin drip. Where the hemorrhage is severe, the cervix is hard and closed, C S may be necessary to save the baby, to control hemorrhage, and to prevent afibrinogenemia.

Toxemia of Pregnancy

1.) Preeclampsia and eclampsia.
2.) Essential hypertension.
3.) Chronic nephritis.

Toxemia of pregnancy may require termination of the pregnancy before term. In most cases induction of labor is the method of choice. When the cervix is not ripe and induction would be difficult, C S is preferable.

Fetal Reasons

1.) Fetal Distress: Antepartum fetal distress (FD) may be anticipated in certain high-risk situations such as hypertension, toxemia of pregnancy, diabetes, intrauterine growth retardation and postmaturity. In these instances, a positive oxytocin challenge test, as indicated by the production of hypoxic deceleration (type II dips; late deceleration) would imply that the fetus is not capable of withstanding the more vigorous contractions of normal labor. Such pregnancies should, therefore, be terminated by C S.

Intrapartum FD may be anticipated when patients with the aforementioned complications begin labor. Premature labor, placenta previa, abruptio placenta, oxytocin induction or stimulation of labor may be associated with FD. The passage of meconium in labor may well be indicative of a low fetal PO_2 and therefore of FD. Any of the aforementioned circumstances would be an indication for the use of fetal monitor during the intrapartum period.

The preponderance of evidence shows that fetal monitoring is predictive of fetal hypoxia, will slightly increase the C S rate, and will decrease the perinatal mortality. It would be an incorrect assumption that fetal monitoring and more liberal use of C S were solely responsible for the improvement in perinatal outcome, as other improvements in the postnatal management of these babies in the intensive care nursery also had a salutary effect.

Internal fetal monitoring with a scalp electrode is superior to an external transducer. Beat-to-beat variability, a sign that the fetus is responsive to its chemoreceptors and baroreceptors, cannot satisfactorily be shown except by fetal EKG.

Recurrent episodes of hypoxic deceleration on monitor tracings imply that the fetus is hypoxic due to poor intravillous space perfusion. Cord compression decelerations (variable decelerations, type III dips) are indicative of umbilical cord compression. Attempts to reverse these patterns by changing position of the mother, supplying oxygen to the mother, decreasing uterine activity and correcting maternal hypotension are useful. Should umbilical cord compression be suspected, sterile vaginal examination is mandatory to rule out occult cord prolapse. Hypoxic decelerations and cord compression decelerations are more ominous when accompanied by reduced or absent fetal heart rate variability.

Fetal hypoxia, suspected by changes in the fetal heart rate tracings, may be confirmed by pH determination of fetal scalp blood. After appropriate therapeutic interventions, a pH of ≤ 7.25, in the absence of maternal acidosis, would justify termination of pregnancy, probably by C S.

2.) Previous Fetal Death or Damage: Especially in older women who have given birth to more than one dead or damaged baby, C S may be elected.

3.) Prolapse of the Umbilical Cord: In the presence of an undilated cervix, the condition is managed best by C S, provided that the baby is in good condition.

4.) Maternal Diabetes: The fetus of the diabetic mother is inclined to be larger than normal and this can lead to difficult labor and delivery. Although these infants are large, they behave like prematures and do not withstand well the rigors of a long labor. Death during labor and in the postnatal period is not uncommon. In addition, a number of babies die in utero before term has been reached. Because of these dangers to the fetus and because a high proportion of pregnant diabetics develop toxemia, the pregnancy should be terminated by the thirty-seventh week of gestation. When conditions are favorable and a rapid and easy labor is anticipated, induction of labor can be carried out. However, in primigravidas, and in multiparas with a long, closed cervix or a bad obstetric history, C S is the method of choice.

5.) Rhesus Incompatibility: When a fetus is becoming progressively damaged by the antibodies of a sensitized Rh-negative mother and when induction and delivery per vaginam would be difficult, the pregnan-

cy may be terminated by C S in selected cases for fetal salvage.

6.) Portmortem Cesarean: Rarely, a live baby can be obtained if rapid C S is performed immediately after the death of a pregnant woman.

Miscellaneous

1.) Elderly Primigravidity: While the age varies from 35 to 40 years, other factors are equally important. These include the presence or absence of a good lower uterine segment, the elasticity or rigidity of the cervix and the soft tissues of the birth canal, the ease of becoming pregnant, the number of spontaneous abortions, the fetal presentation, and the coordination of the uterine powers. When all these points are favorable, vaginal delivery should be considered. When the adverse factors are present, C S may be the wiser and safer procedure.

2.) Previous Vaginal Repair: e.g. of cystocele, rectocele.

3.) Congenital Uterine Anomaly: Not only does an abnormal uterus often function poorly, but in the case of anomalies such as a bicornuate uterus, one horn may block the passage of the baby from the other. In such cases, C S must be performed.

4.) Bad Obstetrical History: When a previous delivery was difficult and traumatic with extensive injury to the cervix, vagina and perineum, or when the baby has been injured.

5.) Post Term Pregnancy: Post term pregnancy associated with aging of the placenta may result in a scrawny and weak baby who does not do well in the postnatal period. When there is good evidence of postmaturity, labor should be induced. If this is not feasible, the rare case is treated by C S.

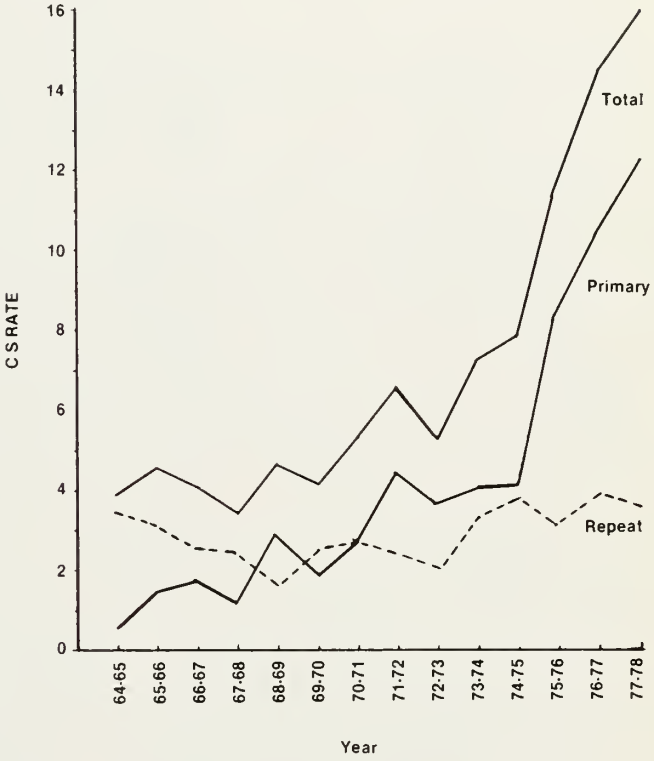
6.) Failed Forceps: It is wiser to turn to abdominal delivery than to drag a baby through the pelvis by force.

7.) Multiple pregnancy may be a valid indication for C S since malposition and/or malpresentation of one or more fetuses may be common. Multiple gestation fetuses are frequently 2500 grams, so that if a breech is presenting in any fetus, the concepts governing breech delivery would apply.

8.) Active Herpes Simplex Virus (HSV) of the genital tract, at term, in a patient with intact membranes would be ample justification for C S in order to prevent exposure of the fetus to HSV in its passage through the birth canal.

There are many reasons for the increasing C S rate. Initially, the availability of safe and adequate anesthesia, whole blood, and even antibiotics, may have been significant factors. Training programs for obstetrician-gynecologists and advances in surgical technique, have made an impact. More recently, however, there is increasing stress on the quality, as well as the quantity of life. The recent data concerning clinical outcome for the newborn and mother have allowed the obstetrician to take a second look at "older concepts". Difficult mid-forceps are no longer recommended. The trial of forceps is considered dangerous. The role of the vaginal delivery of the breech is being challenged. There are new parameters for the diagnosis of fetal distress and uteroplacental insufficiency. All these factors, to a greater or lesser extent, can in part explain the increasing rate of C S.

The C S rates at Central Maine Medical Center for the past 14 years are reviewed. The rate was relatively constant in the 1960s (3.5 to 4.64%). Following fiscal year 1973, there was a continual increase in the C S rate.



The medical records were examined with reference to indications for C S. Only one indication was recorded for each C S. If there was more than one indication, the most relevant one was recorded. The absolute and relative increase in the primary C S rate occurred for two specific indications: cephalopelvic disproportion, and breech position.

The reasons for the increase in primary C S due to cephalopelvic disproportion require further investigation. The author believes that traumatic vaginal and difficult forceps deliveries are no longer being performed. The use of the labor graph has permitted a more scientific approach to both the diagnosis and treatment of labor dysfunction and CPD. At the same time, we are able to institute more prompt and less traumatic methods of management. These methods frequently require C S.

In the United States, the average C S rate 10 years ago was 3 to 8%, whereas today it is 9 to 12%, with some being 15-18%. A change in attitude has occurred; formerly the focus was on the mother and the delivery, but now it centers on fetal outcome. Perinatal death rates were the yardstick by which quality of an obstetric service was measured. More recently, with the availability of sophisticated fetal

monitoring and fetal biochemical tests, the obstetrician and perinatologist have been able to document fetal hypoxia and sort out those fetuses at risk of brain injury. Consequently, the incidence of learning disability, mental retardation and other handicapping conditions has become the standard for measurement of quality of an obstetrical service. Some services are reporting rates as high as 25%, and may regard these as excessive: yet such a rate might be appropriate under certain conditions.

The modern literature contains several reports of large series of cases, some of which are without a single maternal death. Although a study of maternal mortality statistics reveals a high percentage of deaths associated with C-Sections, it is not the operation itself, but other factors—medical and obstetrical complications—that contribute mostly to the mortality. Regardless of the decrease in C S risk, it is well to be reminded that deaths following uncomplicated labor and delivery have likewise been markedly reduced. These differences in relative risk are more pertinent to the question of the advisability of performing the primary C S than to the choice between repeat C S or pelvic delivery.

Few authors have had the audacity to examine the drawbacks of the C S rate.

Drawbacks

The drawbacks of C S must be considered for both maternal and fetal aspects. Maternal penalties associated with C S are increased financial costs and increased maternal mortality and morbidity.

With C S, length of stay in the hospital is doubled over length of stay following vaginal delivery. In addition, operating room costs, additional costs for anesthesia and for the obstetrician increase the financial burden of the patient.

Part of the increased maternal morbidity and mortality is due to the obstetrical complication which led to the C S, but part is due to the surgical procedure itself. Sepsis and hemorrhage account for most of the morbidity associated with C S, as well as the end point of serious morbidity, mortality. Hemorrhage frequently necessitates the need for blood transfusion. Blood itself is a scarce commodity, costly to use, and subjects the recipient to risks of hepatitis and transfusion reaction.

Maternal mortality associated with C S has been reported at 4-8 per 10,000. In one study the risk of dying was 27 times greater with C S than with vaginal delivery. Epidemiologic factors associated with C S maternal deaths were obsesity, grandmultiparity, and age. In addition, prolonged labor, prolonged ruptured membranes, the number of vaginal examinations and low socioeconomic status of the patient were factors associated with sepsis.

Another problem associated with primary C S is risk to mother and fetus in subsequent repeat C-Sections. In recent years, with patients choosing a smaller family size and electing tubal ligation after fewer pregnancies, it is unusual to encounter women having more than three C-Sections. However, each C S subjects the patient to all the risks of C S.

Iatrogenic fetal risk with elective repeat C S is primarily due to poor timing of surgery, resulting in delivery of an infant with an immature pulmonary tree. Elective delivery by C S at 37 to 38 weeks is associated with a tenfold increase in hyaline membrane disease over those infants delivered by the vaginal route.

Conclusion

C S has changed from an operation of necessity to one of choice, with improved maternal results and certainly with better fetal outcome. The operation is not without drawbacks, however, and the critical question is that of determining the point of optimal benefit-cost ratio. Exactly where that point lies is the great controversy of modern obstetrics. It is doubtful that any specific C S rate can be considered high or low or optimal as a general rule, for the important factors in this determination vary so greatly in their frequency.

Although attitudes toward C S have changed radically and indications have been more liberal, wide variations in the use of C S within the practices of physicians sometimes reflect the status of their knowledge and judgement, rather than the nature of their practices. Periodic review of all primary C-Sections is a useful and desirable function in any hospital providing maternity care and can identify physicians whose level of information and competence results in either too liberal or too restricted a use of the procedure.

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Hairy Cell Leukemia

Presentation of a Case and Review of the Literature

ROBERT J. DALTON, M.D.* AND LOUIS FISHMAN, M.D.**

INTRODUCTION

Hairy cell leukemia, or leukemic reticuloendotheliosis, was first separated as a distinct clinical entity by Bournacle in 1958.[1] The term leukemic reticuloendotheliosis had been used much earlier by Ewald in 1923 to characterize a form of leukemia.[2] However, as the term is used today, it indicates a disease entity clearly different than the one suggested in 1923. Over the past 20 years, much has been written about this disease. The disease has also been called "neoplastic lymphoid reticulum cells in the blood,"[3] "chronic reticulolymphocytic leukemia,"[4] and "reticulum cell leukemia."[5] All of these disorders would seem to be the same as that described by Bournacle in 1958. To avoid the use of these cumbersome terms, the phrase "hairy cell"[6] leukemia is more aptly applied since in fact it describes the characteristic morphological appearance of the cells in the peripheral blood, that is, the presence of either fine hair-like cytoplasmic projections from the surface of the cells, or thicker and more irregular ones like pseudopods. The incidence of this disease is low, perhaps 2% of all leukemias.[1] The importance of recognizing this disease lies in its therapeutics since customary therapy for leukemia, i.e., chemotherapy, is not well-tolerated by patients with this disease entity.

The presentations of this disease can be varied and in fact patients with this disease tend to be referred to larger institutions because their disease does not conform to the more easily recognized patterns of malignant hematologic disease. It is often thought to be an atypical lymphoproliferative disorder. The cells circulating in the peripheral blood are unusual, being neither blasts nor ordinary mature lymphocytes. There is an absence of peripheral lymphadenopathy. The spleen is often massively enlarged and in fact hypersplenism with pancytopenia may be the presenting pattern without a leukemic picture. Bone marrow aspiration may be impossible to obtain. In fact, it is the unusualness of the presentation that should make one suspect hairy cell leukemia as the diagnosis. Clinically, the disease is not clearly lymphoma, chronic lymphocytic leukemia, chronic lymphosarcoma cell leukemia, or acute lymphocytic leukemia. There is, however, one laboratory test that is rather specific and can be of great help in making the diagnosis. It was described by Yam and Li[7] in 1971 and involves tartrate resistant acid phosphatase staining of the abnormal cells either in the peripheral blood or marrow.

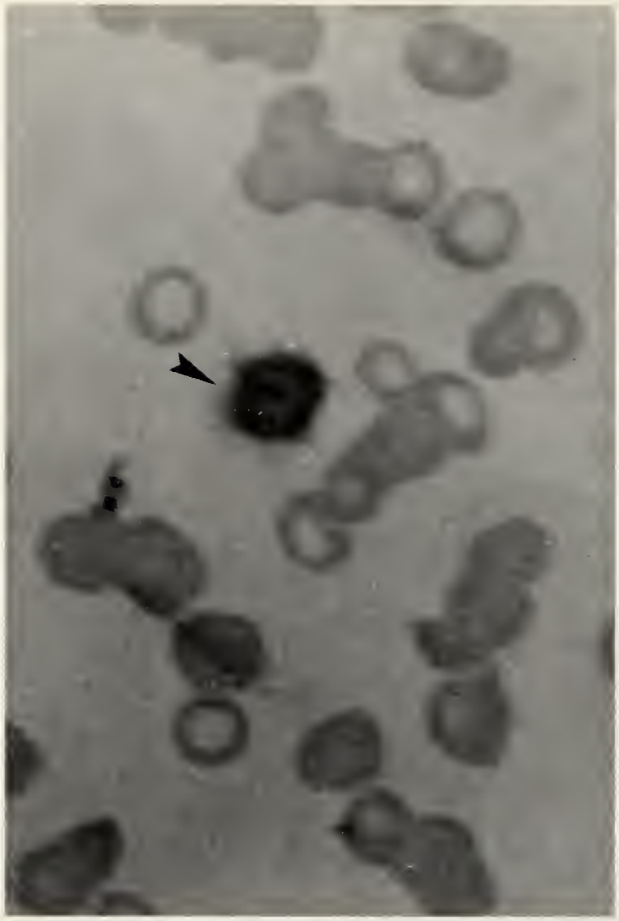
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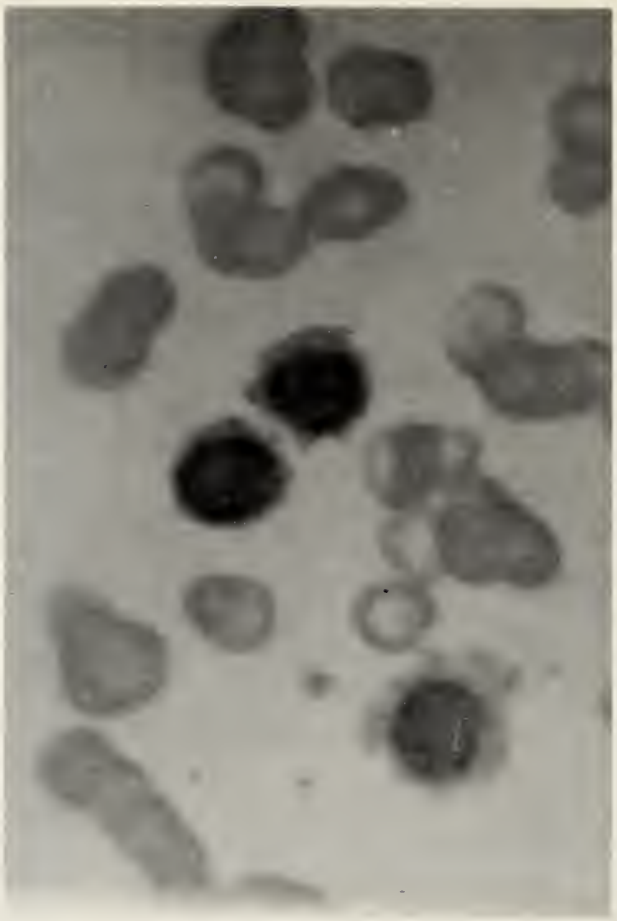
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We here present the case history and clinical course of a 56-year-old male who recently presented with such an "unusual" lymphoproliferative disorder.

CASE REPORT

A.B., a 56-year-old white male, was first seen by his primary physician two years ago for essential hypertension. He was taking Hygroton® 100 mg. daily and Inderal® 80 mg. b.i.d. with reasonable control of his blood pressure. In September of 1977, he had an annual check-up. He was found to have a WBC count of 4,700 with 9% polys and 83% lymphocytes. His sedimentation rate was 44 mm/hr corrected. His liver function tests were normal. He was not seen again until February of 1978 at which time he was feeling relatively well. On August 17, 1978, he was seen in the office with chief complaints of headache, a slight cough and generalized aching of two days' duration. He was afebrile. It was felt that he probably had a viral upper respiratory infection and was sent home on aspirin and fluids. On August 20, 1978, the patient's wife called to say that the patient had spent an uncomfortable night with increasing shortness of breath and a productive cough. He had also experienced night sweats, nausea, loss of appetite and frontal headaches made worse by coughing. An additional complaint elicited was that he had noted easy bruising over the past year. He was examined in the Emergency Room of St. Mary's Hospital in Lewiston. The abnormal findings on his physical examination were dullness and flatness to percussion over the left posterior chest from the sixth rib down. His right lung was clear. His spleen was palpable four finger breaths below the left costal margin. It was firm but non-tender. The liver was not palpable. There were no other abnormal abdominal masses or enlarged nodes. WBC count was 2,100 with a differential of 13 segs, 2 stabs, 1 baso, 2 eosins, 82 lymphocytes and 0 monocytes. Hemoglobin was 7.9 gms. with a hematocrit of 25.5%. Platelets were 51,000/mm.^{3} The peripheral smear showed toxic granulation in the white cells and the presence of "hairy" cells (Figs. 1 and 2). The urinalysis showed 100 mg.% albumin and a 1+ amorphous urates. The prothrombin time was 15.4 seconds with a control of 12.0 seconds. The PTT was 21.4 seconds with a control of 24.4 seconds. Bleeding time was normal. The total bilirubin was 2.05 mgs. with a direct of 1.2 mgs. SGOT was 80 (N-40) and Alk. Phos. 325 (N-300). Creatinine was 2.2 mgs.%. The serum sodium was 138 meq., potassium was 4 meq., chlorides were 100 meq. and the bicarbonate was 29 meq. The total protein was 4.2 megs.%. The glucose was 107 mg.%. The leukocyte alkaline phosphatase score was 184 with normal being 11-95. Serum protein electrophoresis was normal. The sputum cultures showed a normal flora. Chest x-ray showed a left lower lobe infiltration and a left pleural effusion. Thoracentesis showed mainly small lymphocytes. A liver scan was normal. Bone marrow aspiration was dry; however, a small drop of blood was obtained and showed hairy cells. A bone marrow biopsy was hypercellular and diffusely infiltrated by small, darkly-stained cells that were not crowded together (Figs. 3 and 4). A bronchoscopy was negative. A peripheral smear was sent off and tartrate resistant acid phosphatase staining of his lymphocytes was demonstrated. The diagnosis of hairy cell leukemia seemed secure. In the hospital, the patient was first given Erythromycin and later changed to Kefzol® and Gentamycin. All cultures were negative. His condition deteriorated. In view of his splenomegaly and hypersplenism, it was felt that a splenectomy was in order. He was transfused with packed cells to an acceptable level. On the morning of surgery, he was given four units of platelets. A splenectomy was done without incident removing a huge spleen and two accessory spleens. The spleen weighed one gram and was diffusely infiltrated with neoplastic cells. He was given packed cells, fresh frozen plasma and platelets during and following surgery. He had an uneventful recovery from surgery with an improvement of his





Figs. 1 and 2. Patient, A.B., Wrights stained peripheral blood showing atypical cells with cytoplasmic projections.

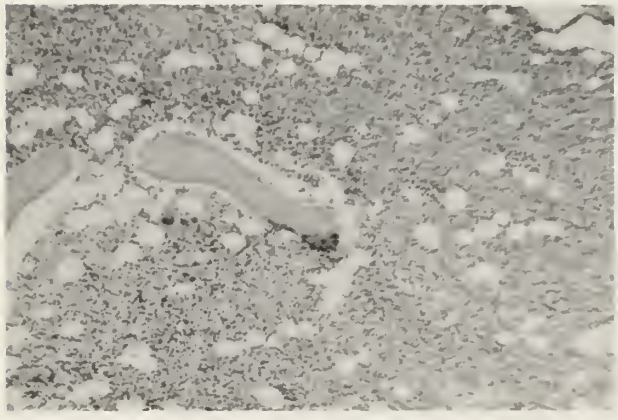


Fig. 3. Patient, A.B., Bone marrow biopsy showing diffuse infiltration with small, darkly-stained cells that are not crowded together. (10X)

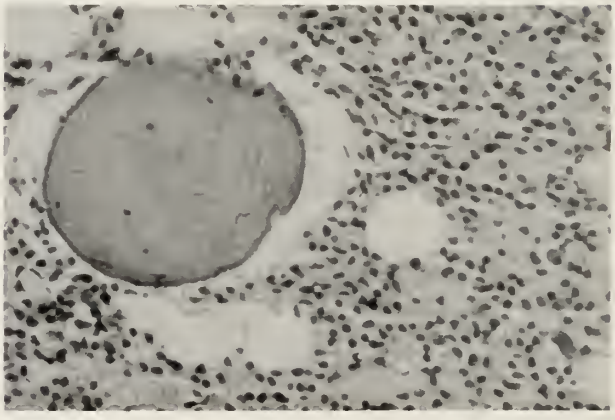
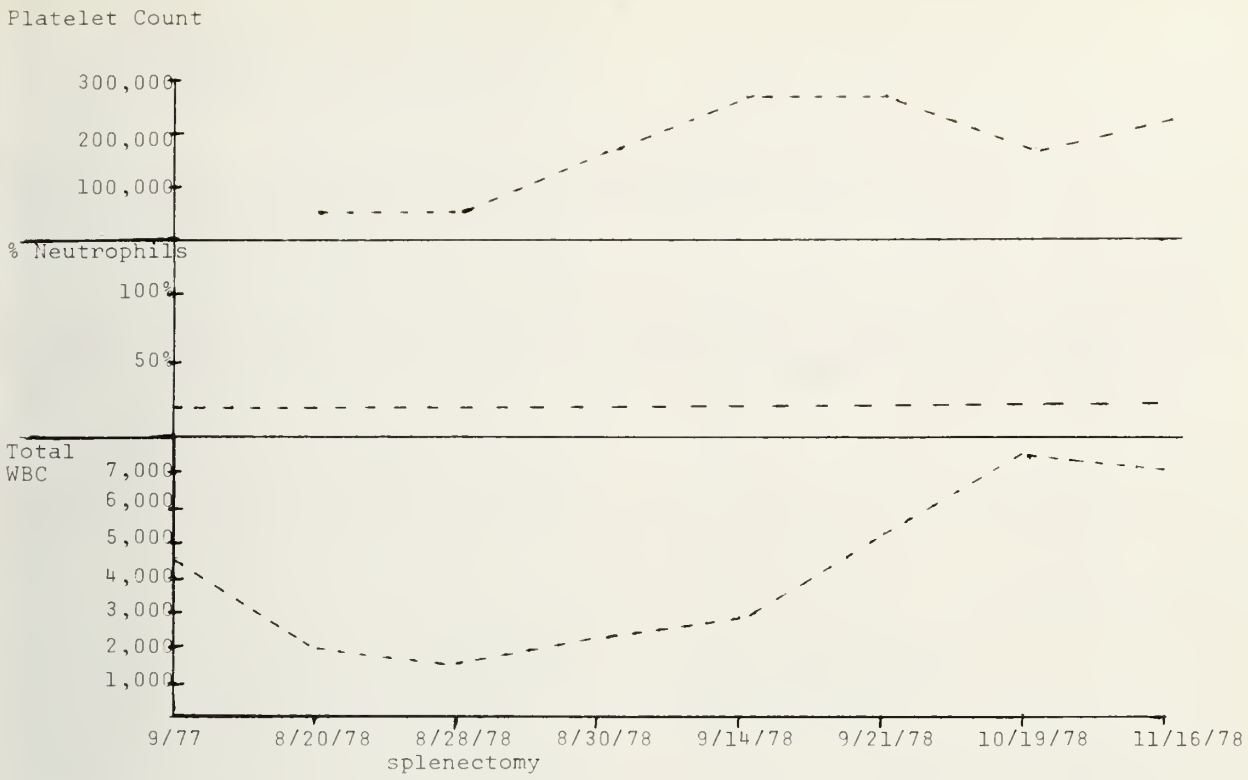


Fig. 4. Patient, A.B., High-power view showing monotonous cellular infiltrate. (43X)

blood picture and chest x-rays. He was discharged on the ninth postoperative day in a significantly improved condition. When seen a month after discharge, he seemed to be doing well. His WBC count was 5,600 with 16% neutrophiles. His hemoglobin was 13.8 gms. The platelets were 272,000/mm.^{3} Chest x-ray revealed continued improvement in his pulmonary infiltrate and his liver function tests had returned to normal (see Table 1).

Discussion

Clinically, the age of presentation ranges from 30 to 80 with a mean of roughly 50 years of age. The male to female ratio is 3-4:1.[8,9] The presenting features are often non-specific in nature consisting of fatigue, vague abdominal complaints or weight loss. If hypersplenism is a significant pathological process, then the symptoms of anemia and/or thrombocytopenia may be manifest. Fever may be a presenting feature without documented underlying infection.[21] If there is heavy organ infiltration by the leukemic cells, then symptoms referable to this infiltrate may be present, such as dyspnea if the lungs are involved. Of course, the patient may be totally asymptomatic and be suspected of having the disease from the finding of abnormal cells on the peripheral smear, abso-



Patient, A.B.: Response of peripheral blood counts to splenectomy. Note % neutrophils remains persistently low.

lute lymphocytosis, or asymptomatic splenomegaly.

Physical findings most consistently demonstrate splenomegaly. Estimates range to 90%.[9] It is frequently massive splenomegaly. Hepatomegaly has been estimated to be present from 25% to 30%. Lymph node enlargement is present in 10% to 24%, but was not massive and usually described as shotty. In fact, if lymph node enlargement is present, it may be limited to one area.[9]

In terms of laboratory findings, the most consistent finding is that of pancytopenia, variously estimated to be present in 50% to 90%[9] of the cases. In most patients, a relative or absolute lymphocytosis will be reported. Interestingly, in 1976, Seshadri reported a definite monocytopenia in five cases of hairy cell leukemia.[11] Even if thrombocytopenia is not part of the clinical picture, there may be qualitative abnormalities in the patient's platelets.[12] Patients may be frankly leukemic with WBC counts ranging up to 127,000[13] with the majority of cells being abnormal appearing mononuclear cells. The diagnosis can be suspected alone from the characteristic morphology of these cells in the peripheral blood. The diameter of these cells ranges from 10-15 microns. With the Wright Geimsa stain, the cytoplasm is pale blue and characteristic fine filamentous projections were observed at the cytoplasmic surface. The nucleus is sometimes eccentric and may be oval or indented with loose, lacy chromatin and have 1-2 nucleoli.[6] The percentage of these cells in the peripheral blood ranges from 2% to 90%.[9] If there is liver infiltration to a significant degree, tests of liver function will be abnormal.[10] In fact, infiltration of kidneys, adrenal glands, stomach, pancreas and small intestine have been reported,[1] hence blood test abnormalities referable to many organ symptoms may be present. Bone marrow aspiration wil be "dry" in 50% of the patients.[9] However, even if the aspirate is dry, some material may be obtained from the end of the needle. Smears of this material will frequently be rewarding in showing the presence of hairy cells. Bone marrow biopsies, however, show characteristic patterns of involvement. There may be either focal or diffuse infiltration with mononuclear cells that are not tightly packed together as opposed to the crowding so typical of lymphomatous or leukemic involvement.[14] Reticulin stains of marrow biopsies may show increased amounts of reticulum in certain areas. The spleen also shows a distinctive pattern of involvement in that the cellular infiltrates originate in the red pulp and expand to replace the white pulp. This is in contrast to lymphomatous involvement of the spleen where the white pulp is preferentially involved. Malignant histiocytosis and nonlymphocytic leukemias are the only other processes that may seem to originate from the red pulp. One may also see pseudosinuses in the spleen, that is red blood cells lined by hairy cells.[21] In the liver one may also see angiomatous spaces lined by hairy cells, not endothelial cells.[22] Abnormal cellular infiltrates will be seen primarily in portal triad areas. The differential diagnosis of this pattern of liver involve-

ment includes infectious mononucleosis, malignant histiocytosis and nonlymphocytic leukemias. In 1971, Yam, Li and Finkel demonstrated the presence of tartrate acid resistant acid phosphatase staining in the majority of hairy cells.[7] This corresponds to the isoenzyme 5 demonstrated by disc acrylamide gel electrophoresis. Between 10-100% of the total acid phosphatase activity in hairy cells corresponds to the isoenzyme 5. The percentage of positive hairy cells varies from case to case; only a few cells are positive in some, the majority in others. An inherent control is present in most slides since polymorphonuclear cells will stain positively with acid phosphatase as will the hairy cells. However, when tartaric acid is added, the positivity disappears from the polys but remains in the hairy cells. Some reporters, however, have described cases of tartaric acid sensitive hairy cells.[9] It is also possible that one may have rare instances of tartrate resistant acid phosphatase staining in other diseases, particularly prolymphocytic leukemia.[15] Hence in a case of otherwise typical hairy cell leukemia, the absence of confirmatory tartrate resistance should not defer one from making the diagnosis.

A controversy has arisen regarding whether the hairy cell is of lymphocytic or monocytic-histiocytic origin. The capability of these cells to resynthesize surface immunoglobulin suggests that they are B-lymphocytic in origin.[10,16,17] However, the finding that 25% or more of hairy cells are capable of phagocytizing zymosan suggests a relationship to monocytes. Obviously, further information will be forthcoming on this unusual combination of functions of the hairy cell.

Hairy cell leukemia is usually chronic, sometimes lasting longer than 15 years.[1,6] Medial survival has been estimated to be between two and four years. It should be recognized that patients may have a long, asymptomatic period where hairy cells are present in the peripheral blood before a diagnosis is made. It has been stated that "splenectomy appears to be the best single measure for improving well-being and life expectancy in hairy cell leukemia".[18] However, it is possible today to diagnose the disease at a stage where observation alone may be the best treatment. Patients with minimal splenomegaly and small numbers of hairy cells in the peripheral blood are best left alone and simply followed. However, the usual presentation is that of pancytopenia and splenomegaly. The pancytopenia is secondary to both hypersplenism and also to marrow infiltration by hairy cells. It is this group of patients that particularly benefit from splenectomy.[18] Complete responders to splenectomy, that is those whose counts return to normal, fared better than partial or nonresponders. The median survival for CR's was 34 months as opposed to 6 months for PR's or nonresponders.[18] It would seem that initial spleen size did not predict response to splenectomy. In patients with a clear leukemic phase (i.e., normal or increased WBCs with the majority of WBCs consisting of hairy cells), the role of splenectomy is less clear in terms of overall survival. Certainly anemia and thrombocytopenia may be alleviated and for this reason splenectomy may be appropriate. It would seem, however, that patients with leukopenia and a low percentage of hairy cells, in addition to cytopenias in the other cell lines, are the ones to stand the most benefit from splenectomy.[10]

The role of chemotherapy in this disease is still being assessed. Empirically, the observation that chemotherapy often induces prolonged neutropenia followed by serious and often fatal infections is well founded. Yam reported impaired granulocyte reserve and leukocyte mobilization in these patients irrespective of the presence or absence of a spleen.[19] Hence there is reason why chemotherapy is hazardous in these patients. In patients who have progressed after splenectomy, attempts at treatment should be made.

The role of steroids is controversial. Catavosky obviously feels some improvement may be obtained with short courses of Prednisone.[18] He admits, however, that any benefit is usually short-lived. This opinion must be tempered by Bouza's report suggesting that steroids may predispose this population group to infections.[21]

Most reports have stressed the danger of aggressive chemotherapy in this disease. This may not be because of insensitivity of the hairy cell to the drug, but because of the presence of a severely compromised marrow. Both Catovsky and Golomb emphasize a cautious approach using low dose Cytoxan® or Leukeran® . A reasonable approach would be to use Leukeran in a dose of 4 mg. initially, decreasing to 2 mg. for maintenance. There are, however, recent reports of benefit with aggressive combination chemotherapeutic regimes.[18,20] The clinical course of these patients has been very stormy. The role of chemotherapy in this disease awaits further refinement. Finally, in this therapeutically difficult disease, we should not overlook a possible role for androgens in improving troublesome symptoms of anemia.

In summary, we have presented the case history of a rather "typical" patient with hairy cell disease. The purpose of this report was to acquaint you with this disease as a clinical entity. We would suggest that the diagnosis of hairy cell leukemia be suspected in those patients who present with atypical mononuclear cells in the peripheral blood associated with splenomegaly, cytopenias and the absence of lymphadenopathy.

It is a clinically satisfying disease to diagnose since confirmatory evidence for the diagnosis can be obtained utilizing specific cytochemical staining of the abnormal hairy cells.

Acknowledgments

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Continued on Page 106

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Shoulder Dislocation

An Easier Method Of Reduction

VICTOR M. PARISIEN, M.D.*

Of the many methods of reducing the common anterior glenohumeral dislocation, none has been found to be easier than the method to be described. It requires

1. No anaesthesia-general, I.V. or local.
2. No analgesia-oral or parenteral.
3. No muscle relaxants.

No originality is claimed for this technique. It was taught to me by Dr. Walter Dixon of Norway, Maine who obtained it from Dr. Kenneth Hamilton. It is commonly used in Germany.

MATERIALS

An old style straight back chair without arm rests is required the back of which is padded with a bath blanket. In modern emergency rooms, this type chair is often not available so an ordinary low back modern chair without arm rests with a padded wooden crutch inserted in front of the back rest of the chair and behind the seat, can be substituted.

METHOD

The patient sits sideways on the chair with the affected arm draped over the back rest of the chair and over the crutch if this is used. The crutch has the advantage of adjustability for height. This positioning is technically the most uncomfortable and difficult part of the whole procedure.

Once the patient is as comfortably settled as possible, putting as much of his upper body weight as possible on the crutch, the patient's humerus is slowly externally rotated with his upper extremity held at the elbow and wrist, using the forearm as a lever. This must be a slow, gradual, gentle, external rotation. Jerking movements will only occasion further protective spasm. The patient is reassured during this procedure that no sudden movements will take place and that the pain will soon be over. Traction on the arm is unnecessary and undesirable; the humeral head being inferior to the glenoid in most cases and gravity exerting sufficient downward force. The characteristic thud of reduction is often so gentle as to be barely perceptible. Once the humerus is at 90 degrees of external rotation, the contour of the shoulder is restored and the patients discomfort is lessened dramatically; the humerus is brought back to normal internal rotation and the crutch removed.

DISCUSSION

This method is safe, gentle, painless and effective. Over 130 shoulders have been reduced over the years without a single complication or failure of reduction.



Fig. 1. The position at the moment of reduction.

This has included numerous athletic muscular individuals, a five-day-old dislocation and a three-day-old dislocation.

The reader will notice that this method combines elements of the Kocher maneuver and the Hippocratic maneuver. The major advantage is that the patient can relax more completely when he is sitting and can see what is happening and the weight of the arm and upper body is taken up by the padded crutch. The only force necessary is the minimal amount required to overcome the subscapularis, the other muscles being relaxed. Sufficient pulsion force is provided by the axillary pad to accomplish the reduction.

The advantage of not having to use drugs of any kind is again emphasized.

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Percutaneous Transhepatic Biliary Drainage

Payson S. Adams, Jr., M.D.*

A relatively new nonsurgical technique has been developed to drain the biliary system in the presence of malignant obstructive jaundice. It was first described by Molnar and Stockum[1] in 1974 and has been described and refined by others.[2,3,4,5]

With increasing frequency, we are seeing obstructive jaundice due to carcinoma of the pancreas with more than 20,000 deaths per year. Many palliative bypass procedures to reduce jaundice have been used, but the operative mortality may range for 20.8%[6] to 33%.[7] Postoperative complications may be as high as 43%.[6] The average length of survival of less than 6 months and lengthy hospitalization after surgery makes the undertaking of the surgical procedures a difficult choice. For these reasons, percutaneous drainage of the biliary system appears to be an attractive alternative in an often hopeless situation. The procedure has been a natural offshoot of the development of the diagnostic percutaneous transhepatic cholangiogram using the skinny needle.

Technique

The patient is started on 250 mg. Ampicillin q.i.d., 24 hours prior to the procedure and is maintained for 3 days. The right lateral abdominal wall is prepped and a 19 gauge, 27 cm. long needle with an 18 gauge sheath catheter is advanced into the liver at a point in the mid axilliary line below the costophrenic sinus, usually in the tenth intercostal space. This is done under fluoroscopy and the needle tip is aimed down toward the T-12 vertebral body. The porta hepatis is usually in this position in the mid abdomen. The needle is first withdrawn and then the sheath catheter until free flow of bile is established and confirmed with tests of contrast injections. A guide wire is then advanced through the sheath catheter down the duct and to the point of obstruction. It is generally possible to negotiate the obstruction at this time possibly with the help of a torquable guide wire to search for the lumen. If the obstruction cannot be passed, the sheath catheter is exchanged for a #6.7 French pigtail catheter with several side holes and is parked in this position for 24 hours hooked to external drainage. After this period of time, changes occur secondary to decompression, perhaps reduction of edema, that then allow passage of a guide wire through the obstruction into the duodenum. The catheter is then changed for a Cook #8.3 French Ring biliary drainage catheter with a pigtail end and 40 side holes. This was developed by Ring,[8] who found that the pigtail anchored the catheter in the duodenum and the side holes were the average number needed to drain the usual more distal duct obstructions. This can be tailored to each patient by adding more side holes as needed so that there are an adequate number above and below the obstruction. It is important not to allow the side holes to lie within the parenchyma of the liver, as they could face a vein causing hemobilia. The catheter is then left in place indefinitely. It is irrigated with saline every three days and changed every three months.



Fig. 1. Percutaneous transhepatic cholangiogram showing marked dilatation of the common duct and obstruction.

Case Report

L.P. is a 71-year-old female admitted on September 17, 1978 with a one month history of increasing painless jaundice, anorexia, pruritus, clay colored stools and a 17 pound weight loss. She had slight abdominal distention and no palpable masses. Total bilirubin of 10 mg. per cent, all direct, was recorded. The alkaline phosphatase was 303 units. The urine showed 4 + bile.

Because of suspected carcinoma of the pancreas, a percutaneous transhepatic cholangiogram was done on September 19, 1978 which showed complete obstruction of the common bile duct with dilatation to 27 mm. Transabdominal aspiration biopsies under fluoroscopy were done on two occasions. The first showed normal cells. A brush biopsy through the catheter and into the common duct was then done and was normal. The second aspiration biopsy on September 22, 1978 was positive and consistent with adenocarcinoma of the pancreas. On September 20, 1978, however, a percutaneous biliary drainage procedure was undertaken for the presumptive diagnosis of carcinoma. A catheter was advanced through the biliary system to the site of obstruction in the common duct, but would not pass into the duodenum. After 24 hours of external drainage, the size of the duct system diminished markedly and the catheter was then manipulated into the duodenum.

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Fig. 2. Guide wire advanced through sheath catheter down the duct to the site of obstruction.



Fig. 3. Pigtail catheter parked above the site of obstruction.

On September 21, 1978, her total bilirubin had reached a high of 19.5 mg. percent with a direct of 16.5 mg. percent. The alkaline phosphatase was recorded at 305 units. Internal biliary drainage was thought to have been accomplished.

Because of the extent of the cancer and the elevated bilirubin to nearly 20 mg. percent, surgery was not considered and she was discharged home on September 26, 1978. Home nursing care irrigated the catheter every 3 days.

The patient was re-admitted on October 3, 1978 with a temperature of 104°F and a diagnosis of cholangitis was made. She was started on Keflin® 1 gram q6h and her temperature soon returned to normal. The total bilirubin had fallen to 10.2 mg. percent with a direct of 5.7 mg. percent, but adequate internal drainage apparently had not been well established. A new Ring biliary drainage catheter was then introduced and better drainage was established. The patient was then discharged on October 8, 1978 with catheter irrigation scheduled every 3 days.

A recent outpatient visit on October 30, 1978 found the patient to be clinically free from jaundice with a total serum bilirubin of 2.8 mg. percent.

Discussion

Percutaneous biliary drainage is rapidly becoming a practical alternative to a very depressing situation when the common duct is obstructed by cancer. Although there is probably no prolongation of life, these patients will not die from liver failure due to obstruction. With life expectancy of six months or less, subjecting them to the high morbidity and mortality of palliative surgical procedures and prolonged postoperative hospitalization seems a poor choice. In the case presented, the time between the initial admission, diagnosis and treatment was five days and discharge can rapidly follow.

Initially in this case, a #8 French pigtail polyurethane catheter, in which multiple side holes were made, was used. Unfortunately, the wire mesh of the side walls caused some obstruction of the lumen after the hole punch was pushed through the wall of the catheter. The holes were also rather small in caliber. It was for these reasons that adequate drainage was not initially established and cholangitis ensued. After changing the catheter for the Ring #8.3 French polyethylene catheter made by Cook, internal drainage became adequately established. Catheters as large as #12 French have been used, but they do not seem to give any better drainage. Almost any type of catheter could be used as long as there are enough side holes of adequate size above and below the obstruction. The Ring catheter has a right angle bend just proximal to the pigtail tip. This helps to keep the catheter well down in the duodenum so enough side holes are beyond the obstruction. The pigtail provides a measure of safety so that the catheter will remain anchored in the duodenum. It has been found that sometimes during normal diaphragmatic excursions, the catheter can back all the way out of the liver and some have been found lying along the abdominal wall. In forty-one patients done by Pollock, Ring, Olega, et al,[9] they failed to negotiate the obstruction in only two due to widespread metastasis.

Sometimes tumors at the porta hepatis can cause obstruction of both the right and left hepatic radicals. In this situation two catheters can be introduced, one in the right hepatic radical and the other transabdominally into the left side. Both can be advanced down the hepatic and common ducts into the duodenum. More than two catheters can be used in cases of multiple strictures of sclerosing cholangitis. Instrumentation, such as dilatation of benign common duct strictures, has been done exchanging the drainage catheter for balloon dilatation



Fig. 4. After 24 hours of drainage externally, the guide wire was able to negotiate the site of obstruction.



Fig. 5. After the initial 24 hours of drainage, the catheter is now placed well into the duodenum with multiple side holes above and below the lesion. Notice the marked reduction in the dilated ducts even after such a short period of drainage. Also note the aspiration biopsy needle inserted in the lesion.

catheters. Similar catheter techniques have been used to remove stones in the common duct by introducing ureteral stone baskets through the catheter, snaring them and depositing them in the duodenum.

In the case presented, two aspiration biopsies were necessary to secure the diagnosis. Transabdominal thin needle biopsies have been found to be of little risk and would seem to be a necessary adjunct to the drainage procedure as diagnosis should be confirmed either by this method, or by an open biopsy which one would like to avoid if possible.

Pereiras, et al[5] have recently reported 12 cases where, after establishing catheter drainage, they advanced a short stent through the obstructed segment which was then left in place permanently. They then removed the external drainage catheter. Their results are good to date, but removing the external catheter and losing access to the biliary system may create a problem if obstruction re-occurs above the stent it may not be possible to get back through the area with the stent in place. They feel the external catheter creates patient discomfort. This, however, has been found to be minimal even in some of Ring's[8] very long-term patients. They have even been known to swim with them in place although this is not recommended. They say contamination and sepsis can occur, but this is controlled easily with antibiotics and bile leakage does not seem to be a problem. Obstructed side holes in the catheter will occur, consequently changing the catheter every three months is recommended. This causes little patient discomfort. In Pereiaras', et al short-term follow up, no recurrent obstruction has been recorded, but if the stent's distal end is in the distal common duct, as recommended, then recurrent obstruction must be considered a likely complication. They have not recorded any instance where the stent fell out of the duct, but this is also possible.

Complications are minimal and may include hemobilia probably due to improper catheter placement. Cholangitis occasionally occurs as it did as a late complication of the case presented. This has been easily controlled by antibiotics.

Summary

A case of percutaneous transhepatic biliary

drainage for obstructive carcinoma of the pancreas was presented. The technique of passing a catheter, after a lateral abdominal needle puncture wound and advancing it into the biliary system, past the obstruction and into the duodenum was described.

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Hairy Cell Leukemia: Presentation of a Case and Review of the Literature

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Spring Meeting of the M.M.A. House of Delegates

Saturday, April 7, 1979

Mid-Maine Medical Center (Thayer Unit), Waterville, Maine

12:30 P.M.—Registration; 1:00 P.M.—Lunch; 2:00 P.M.—Meeting

9:30 A.M.—Meeting of the Executive Committee

ABSTRACTS
Fourth Annual Maine Biomedical Science Symposium
The University of Maine at Orono
June 8 and 9, 1978

BEHAVIORAL CORRELATES OF DISEASE PROCESSES AND AGING

WAIS Performance for Different Age Groups of Hypertensive and Control Subjects During the Administration of a Diuretic

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This study examined the effects of age and hypertension on intellectual performance. Previous studies have reported that hypertension adversely effects cognitive functioning, but few have considered the influence of hypertension on discrete age groups. In the initial analysis, hypertension was negatively associated with WAIS Verbal score for Young (21 to 39 years) but not Old (45 to 65 years) subjects. Further Young subjects attained higher WAIS performance scores than did Old subjects. Medication history of hypertensives was not associated with performance levels, nor was performance of controls influenced by whether or not they were tested while on a diuretic. Subsequently WAIS performance scores were analyzed for subjects matched on WAIS Verbal across age (21 to 39 vs. 45 to 65 years) and blood pressure (normotensive vs. hypertensive). A significant age by blood pressure interaction was found. The effect of blood pressure was much greater among Young than Old subjects. In separate analyses, the association between renin level and WAIS Performance was also examined. Contrary to previous findings no association was found between renin level and performance. The results are discussed in the context of previous hypertension research and their implications for comparisons across age levels.

The Effects of Hypertension and Age on Specific Tasks of the Halstead Neuropsychological Test Battery

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The purpose of this experiment was to determine the effects of age and hypertension on the performance on the Halstead Neuropsychological Test Battery. All hypertensive subjects had blood pressure (BP) readings greater than 140/90. The hypertensive subjects were either medicated or unmedicated depending on their past antihypertensive medication history. The normotensive subjects were recruited from the community (BP $<$ 140/90). The subjects were divided into two age groups: 22-36 years and 48-64 years. All of the subjects were tested on the Category Test, the Tactual Performance Test and the Tapping Test and a Brain Impairment Index (II) generated from these tests. The older age group performed more poorly on the Category Tests, the TPT Total Time, TPT Localization Score, than the younger age group. However, there was no significant difference in II scores between the two age groups. The medicated hypertensives had a higher II score than the normotensive control group, however, this score only approached significance ($p < .06$). The medicated hypertensives performed more poorly on the Category Test, the TPT Memory and TPT Localization scores. For the II and the individual Halstead Tests, the unmedicated hypertensives were intermediate in performance between the medicated hypertensives and the normotensive controls. The poorer performance of the medicated hypertensives suggests that antihypertensive medication effects the performance of hypertensives through direct action of the medication. The II scores of these medicated hypertensives were not characteristic of brain damage; therefore, there was no evidence of a decreased CNS integrity.

Physical and Psychological Differences Between Hypertensives and Normotensives as Measured by the Cornell Medical Index

W.G. WOOD, Program on Aging, Bangor Mental Health Institute, Bangor, ME 04401

Previous research has shown that there is a positive correlation between symptoms reported on the Cornell Medical Index (CMI) and blood pressure values for hypertensives. However, it has not been determined whether hypertensive subjects report more physical and psychological symptoms than do normotensive subjects. This study compared young and old hypertensive and normotensive subjects on the number of symptoms reported on the CMI. The hypertensive subjects had more physical and psychological complaints than did the normotensive subjects. Differences in symptom reporting between the blood pressure groups were not concentrated in one specific category (e.g., cardiovascular) but were distributed over several categories. Females reported more symptoms than males, and female hypertensives reported the greatest number of symptoms. Age did not influence the number of symptoms reported for either blood pressure group. The results were discussed in the context of the lack of specificity of symptoms reported by hypertensive subjects, and to what extent reported symptoms on the CMI are influenced by knowledge of one's blood pressure status.

A Novel Approach to Control of Hypertension in a Rural Maine Community

MARY J.C. BLASCHKE, JAMES S. HUSTON and PETER A. RASMUSSEN, Department of Biochemistry, University of Maine, Orono, ME 04473

Hypertension is the most common chronic disease in the United States, affecting at least 15% of the adult population. In spite of the mounting evidence that hypertension is the most significant known risk factor in the development of strokes, congestive heart failure, renal insufficiencies, atherosclerotic phenomena and arterial lesions in general, the present status of control demonstrates that hypertension is largely a neglected phenomenon. Two major requirements for the improvement of wide scale hypertension control ultimately involve community action. First, massive organized screening programs will be necessary to detect the hypertensive population and secondly, hypertensives must be motivated to accept and comply with medical treatment. Our goal is to stimulate community interest and involvement in this problem with hypertension control programs which minimize the factors that presently hinder compliance. We have designed such a hypertension screening and follow-up treatment program for a rural Maine community, independent of a medical center. Our hypertension control system involves local agencies, mass media, major industries and volunteer services from the community. Although this program is not yet in effect, we anticipate that widespread availability of similar programs will yield major health and economic benefits for large numbers in our society.

Maintenance Treatment of Recurrent Affective Disorders

WALTER R. CHRISTIE, Department of Psychiatry. Maine Medical Center, Portland, ME 04102

The rise in stature of biological psychiatry has given new objective dimensions to the diagnosis of depression. Many forms of depression respond to tricyclic antidepressants. In elderly patients, new findings of brain neurochemistry correlate with descriptive diagnosis and the response to tricyclics. In adult patients, in general, we are gaining clinical perspectives on a large number, perhaps two million U.S. citizens, who have recurrent biologically induced depressive episodes.

The Maine Medical Center is participating with the Psychopharmacology Research Branch of NIMH in a national collaborative study of "Maintenance Treatment of Recurrent Affective Disorders." This double blind study utilizes Lithium Carbonate and Imipramine individually, in combination, or with placebo to determine if both unipolar and bipolar recurrent affective

disorders can be attenuated or prevented. Changes in dosage during recurrence and multiple family and demographic variables will also be examined to identify diagnostic patterns.

The study format will be reviewed along with anecdotal observations on clinical issues raised in its first year of operation.

Does Receptor Supersensitivity Accompany Depressive Illness

M.J. FRIEDMAN, Veterans Administration Hospital, White River Jct., VT 05001

This experiment tests the hypothesis that disuse supersensitivity develops at adrenergic receptor sites during depressive illness. This hypothesis is deduced from the catecholamine hypothesis of affective illness which postulates that depression is associated with a functional deficiency in catecholaminergic activity. The method is a pharmacological bioassay technique applied to a clinical population in which the systolic pressor response to tyramine, norepinephrine and phenylephrine is tested in depressed patients and nondepressed, nonanxious controls. Depressed patients were significantly more sensitive to sympathomimetic agents than the control group. These results are also compatible with the hypothesis that depression is associated with a generalized physiological state of hyperarousability.

Depression and Hypertension

M.J. FRIEDMAN and P.L. BENNET, Veterans Administration Hospital, White River Jct., VT 05001

The study consisted of 1101 Caucasian, male outpatients, who were screened for depression and hypertension in order to test the hypothesis that there is a unique relationship between these two illnesses. Depression was assessed by the Zung Self-Rating Depression Scale (SDS) while diastolic blood pressure (BP) was accepted as the index of hypertension. Medical records were reviewed to determine whether the patient's clinical diagnoses would have an effect on any relationship between depression and hypertension. It was found that there was no correlation between elevated scores on the Zung SDS and diastolic BP. The diagnosis of anxiety, however, was significantly associated both with depression and hypertension.

Depression, Hypertension, and Serum Dopamine-Beta-Hydroxylase Activity

M.J. FRIEDMAN and J.M. STOLK, Veterans Administration Hospital, White River Jct., VT 05001

Serum dopamine-beta-hydroxylase (DBH) activity was measured in a heterogeneous sample of 290 outpatients awaiting medical, surgical, or psychiatric appointments at a Veterans Administration Hospital. All patients were assessed for depressive symptomatology by the Zung Self-Rating Depression Scale (SDS) and for elevated diastolic blood pressure (BP $>$90mm Hg). Elevated DBH activity was associated with SDS scores $>$60. No statistical association was found between DBH activity and diastolic BP. Two pharmacological agents, α-methyl-DOPA and minor tranquilizers, also were associated with significant alterations in serum DBH activity.

A Review and Description of Ongoing Studies of Cognitive Behavior of Angina Syndrome Patients with Normal Arteriograms

F.C. BLOW and M.F. ELIAS, Department of Psychology, University of Maine, Orono, ME 04473

Since the advent of clinical applications of cine arteriography, considerable interest has focused upon reports indicating that angina pectoris-type symptoms may be encountered in patients with normal arteriograms in the absence of other types of cardiovascular disease. However, little information regarding personality variables, cognitive patterns and life stress events is available for patients who have angina pectoris-like symptoms but who do not exhibit clinically significant stenosis of the coronary arteries. In addition to brief review of previous studies, we describe an on-going investigation of behavioral differences between 1) individuals with angina pectoris symptoms associated with stenosis of one or more coronary arteries, 2) individuals with

Continued on Page 109

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angina pectoris-like symptoms but with angiographically normal arteries, and 3) individuals that are asymptomatic (healthy controls). During the subjects' hospital visit (prior to heart catheterization), the MMPI, portions of the WAIS, the Spielberger State and Trait Anxiety Scale, the Zung Depression Scale and the Cornell Medical Index are being administered. Demographic, clinical medical and medical data are also being collected at this time. When the subject returns home, a repeat of the in-hospital testing is given along with the Halstead Categories Test and the Life Stress Events Questionnaire.

Validation of a Short-Form of the WAIS for Geriatric Patients

J.E. BURNS, Program on Aging, Bangor Mental Health Institute, Box 926, Bangor, ME 04401

Satz and Mogel (1971) developed and validated a WAIS short form which included items from all subtests. Their subjects, however, were not elderly. Thus, the need for the present validation study. While there are other short forms, they do not use all the subtests. Such short forms are therefore of limited use if interpretation of subtest scatter is deemed important. Results of this study confirmed that the Satz and Mogel abbreviated WAIS given to institutionalized geriatric patients yielded scores that closely approximated standard WAIS scores. The degree of approximation was equivalent to that obtained with younger subjects. Not only was administration time halved, but the geriatric patients seemed less fatigued by the testing and less likely to react negatively to it.

Ishemic Cerebral Vascular Disease

C.P. OSGOOD, Eastern Maine Medical Center, Bangor, ME 04401

Stroke is the third leading cause of death and morbidity in the United States. Many stroke patients have premonitory symptoms prior to development of established or permanent stroke—these transient episodes of neurologic dysfunction are termed TIA's (transient ischemic attacks). Using modern diagnostic techniques such as cerebral blood flow analysis, measurement of the retinal artery pressures, and ultra sound auscultation of the carotid artery system often will reveal arterial disease or destruction. Normal values for cerebral blood flow would be discussed as well as significant deviations from these values. Recent developments in microsurgical technique have enabled us to bypass obstructing atheromatous lesions of major intracranial arteries. Initial results for this type of bypass surgery have been very encouraging. The patency rates for these anastomoses have been satisfactory and to date the post op incidence of stroke seems definitely reduced. Several cases from our recent experiences at EMMC are presented, in the current state of the art discussed.

CANCER

Nonrandom Chromosomal Aberrations Associated with Human Leukemia

P.H. LAMARCHE, T. MENDOZA and L.J. BEAUREGARD, Genetic Program, Eastern Maine Medical Center, Bangor, ME 04401 and Genetic Laboratory, Rhode Island Hospital, Providence, RI 02902

Cytogenetic studies were performed on over 500 direct bone marrow preparations from patients having preleukemia and leukemia. Studies included "routine" Giemsa stained chromosome preparations and, more recently, "banded" chromosome preparations utilizing trypsin and fluorescent dyes. More than 15,000 cells were studied for aneuploidy and structural chromosome anomalies. The following statistically significant data were obtained: 1) B, C, and G group chromosomes were nonrandomly involved ($p<0.05$) in numeric and structural aberrations, and 2) there was no statistically significant difference between the acute leukemias and the chronic leukemias regarding hypo- or hyperdiploidy. There was no significant increase in the percent of chromatid gaps or breaks as compared to normal peripheral blood controls. Banding studies revealed that the nonrandom chromosomes involved were numbers 5, 7, 9, 21 and 22. These data indicate that 60% of preleukemic or frankly leukemic individuals have significant detectable numeric or structural chromosome aberrations. Viral and chemical oncogenic models in animals also indicate a nonrandom correlation between the mutagen and the affected chromosome.

Recent Advances in the Classification and Management of Acute Leukemia

ARTHUR T. SKARIN, Associate in Medicine, Sidney Farber Cancer Institute; Assistant Professor of Medicine, Harvard Medical School, Boston, MA.

The improved prognosis in acute leukemia during the past 10 years is a result of multiple factors including new chemotherapeutic agents and combination chemotherapy programs, improved dose schedules, intensive treatment during remission, CNS prophylaxis, and vigorous supportive care. Prior to 1948, when methotrexate was introduced by Dr. Sidney Farber, 50% of patients were dead within 3 months and 90% in 1 year. Presently, greater than 50% of patients with acute lymphocytic leukemia are disease-free at 5 years and probably cured. Obstacles to cure in the remaining 50% of patients include drug resistance, inadequate drug distribution accounting for meningeal relapse, a slight but definite morbidity to treatment and pessimism leading to inadequate treatment.

Acute leukemia is classified as either lymphocytic or non-lymphocytic. Based upon histochemical, immunological, and biochemical studies, the former is subdivided into acute undifferentiated, null cell, T-cell, and B-cell types while the latter is divided into acute myelogenous, monocytic, monmyeloid, promyelocytic and DiGuglielmo's types.

Therapeutic results from the Sidney Farber Cancer Institute in acute lymphocytic leukemia of childhood employing vincristine and prednisone coupled with an anthracycline and Asparaginase for induction, combined with cranial irradiation, intrathecal methotrexate and consolidation treatment, reveal a complete remission rate of 94%. The disease-free survival at 4 years is approximately 60%. Results of therapy of acute non-lymphocytic leukemia both in adults and children, employing vincristine, adriamycin, prednisone and Ara-C for induction followed by a multiple drug maintenance program, reveal a complete remission rate of 70% with a median response duration exceeding 2 years. Both studies are ongoing and compare favorably to other combination programs.

Future studies involve application of cell kinetics, absolute leukemic infiltration data, immunologic, biochemical and in vitro growth patterns to identify subgroups which may require more intensive therapy. In addition the role of non-specific immunotherapy with BCG, active immunotherapy employing leukemic cells, and use of a specific antiserum is under investigation.

Serial Monitoring of Serum AFP and HCG in Germ Cell Tumors

DONNA K. THOMPSON and JAMES E. HADDOW, Foundation for Blood Research, Scarborough, ME 04074

Serum AFP and HCG were determined serially by radioimmunassay or electroimmunoassay in 18 males with germ cell tumors. Elevated serum ATP was associated with embryonal cell and yolk sac tumor elements, elevated serum HCG with embryonal cell and choriocarcinoma tumor elements. Neither the presence or absence of serum markers nor the degree of serum marker elevation was associated with tumor stage at initial evaluation. Serial measurement of serum markers correlated with clinical disease course. In all cases without tumor recurrence after treatment, serum markers fell to and remained normal. In the four patients who developed recurrent disease, serum AFP or HCG became elevated 8 to 29 weeks prior to clinical recurrence. Serial serum AFP and HCG determination are a sensitive method for following patients with germ cell tumors. Serum AFP ½ life was determined in 5 patients and may be a useful adjunct to staging germ cell tumors as well as being even more sensitive than actual serum AFP value in detecting pre-clinical disease.

Markers in Breast Cancer

BRUCE PONDER, Senior Fellow, Sidney Farber Cancer Center, Boston, MA

There have been claims that a number of different markers are related to tumor burden in breast cancer. In theory these markers might be used to select patients with apparently localized disease for adjuvant chemotherapy, to predict relapse before it is clinically manifest, and to reassess the response of disease to treatment. In practice, they have so far found little application. The data which are available will be reviewed to determine the part, if any, which these markers might play in the current management of breast cancer.

CELL AND MOLECULAR BIOLOGY

Studies on the Cultivation of Mouse Prostatic Epithelium

P.F. WARD and C. WAYMOUTH, The Jackson Laboratory, Bar Harbor, ME 04609

Our goals in culturing prostatic cells from inbred strains of mice are (a) to select the strains of mice most suitable for primary culture of epithelial cells, (b) to achieve disaggregation of the epithelial cells from the stromal elements, (c) to define the optimal conditions for primary culture, and (d) to develop a cell line of prostatic epithelium. Disaggregation has been achieved enzymatically with 1 mg/ml collagenase and 0.4 mg/ml deoxyribonuclease. This method yields small clumps of cells which attach to plastic culture vessels (Costar cluster 24-well dishes) and spread within 48 h. In our search for optimal conditions for culture, we have devised a chemically defined medium (without serum) which appears to support epithelial cells. In this medium, the usual 26mM bicarbonate buffer system has been replaced with 26mM $Na_2\beta$ glycerophosphate. The Na/K ratio has been increased to 50 from the ratio of 38 in Waymouth's MAB87/3. The hormone supplements are 8.0 μg/ml insulin, 2.0 μg/ml hydrocortisone and 10 μg/ml 5 a dihydrotestosterone. Inclusion of 5.0 μg/ml transferrin and 0.1 g/ml spermine in the medium appear to aid spreading and attachment. The disaggregation and culture procedures, media formulation, and the resulting cell cultures will be discussed.

Mechanisms of and Mechanisms Regulating the Circadian Rhythm of Chick Pineal Serotonin Acetyltransferase Activity In Vitro in Organ Culture

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The pineal gland of chicks maintained under a diurnal cycle of lighting exhibits a marked diurnal variation of serotonin acetyltransferase activity.

We have simulated this cycle *in vitro* with organ cultures of explanted glands, and shown the latter to be directly photosensitive *in vitro*.

Evidence of two mechanisms regulating the cycle will be presented.

Herpes Simplex Virus Reproduction in Normal and Cystrophic Human Skin Fibroblasts

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Several lines of evidence indicate that herpes simplex virus (HSV) requires an intact envelope for maximum infectivity. Alteration of the composition/structure of the viral envelope, which is derived from nuclear membranes, may have significant consequences in infectivity involving interaction with the host cell plasma membrane. In order to determine the specific role of the envelope in the infection process and to understand its importance in determining such things as host range, we have examined the infectivity of HSV type 1 in human skin fibroblasts with genetically-determined membrane defects (Duchenne's muscular dystrophy). When the infecting HSV is produced in HEp-2 cells (HSV-HEp), yields of virus from dystrophic fibroblasts (HSV-DF) are typically 3 to 10-fold lower than from normal fibroblasts (HSV-NF) as determined by plaque assay using rabbit kidney cells (RKC). The time course of viral reproduction in the different fibroblast lines does not differ significantly. ^{3}H-labeled HSV-HEp adsorbs with equal efficiency to both normal and dystrophic cells, suggesting altered entry or early processing of parental virus or infectivity of progeny in the plaque assay. Adsorption of ^{3}H-labeled HSV-DF and HSV-NF to the fibroblast lines and to RKC should help to explain the varying virus yields. Cross infection studies are being performed with HSF-DF and HSV-NF in normal and dystrophic host cells. Preliminary date indicate that HSV-DF productivity in normal fibroblasts is in the order of 100-fold lower than with HSV-NF. Also, initial biochemical studies of the membranes involved in infection will be discussed.

Development of Nutrient Transport in the Chick Intestine

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A tissue accumulation technique was used to measure nutrient uptake in the jejunum of the developing chick. B-alanine uptake was negligible in the embryonic stage, but showed significant accumulation on the day of hatching with a rapid increase until it peaked at 5 days of postnatal life. Uptake gradually decreased thereafter to adult levels. At 18 days of incubation, proline uptake was negligible at the B-alanine transport site but significant at the leucine transport site. Postnatal uptake of proline at the B-alanine site peaked at 2 days and maintained that level at 3 weeks of age. Choline transport was highest at 18 days of incubation. Transport gradually decreased to a low point at 3 weeks of postnatal life. The Ki value of proline on B-alanine transport and the reciprocal, did not significantly change at 2 days and 21 days of postnatal life.

Platinum Blue Anticancer Drugs

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The blue platinum complexes "PtA_2Cl_2" (A = acetamide or trimethylacetamide) are of special interest because they are thought to be similar to the anticancer agents known as Platinum Blues. The nature of "PtA_2Cl_2" has been further elucidated by correlation of spectral data (absorption, luminescence, magnetic circular dichroism measurements) with molecular orbital calculations. The intense blue color of these complexes is noteworthy since platinum compounds usually display pale colors. Chemical means were also used to characterize these blue complexes. In particular, the results of titrations with Ce (IV) to infer the oxidation state of the platinum atom will be reported. The well characterized blue platinum α-pyridone complex, reported recently by S.J. Lippard and co-workers (J. Am. Chem. Soc., *99* (1977) 2827), was also studied by these techniques, and the results are compared with those for the other platinum blues.

(This research was supported by the American Cancer Society).

The Discocyte-Spherocyte Transformation of the Mammalian Erythrocyte and its Implication for Plasma Membrane Organization

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The discocyte-echinocyte transformation has been used by several groups to refine models of red cell membrane organization and specifically to define how the extrinsic membrane proteins, spectrin and actin, might generate changes in cell shape. In many instances, however, the echinocytic stage is *not* an endpoint, and with greater perturbation such crenated cells are transformed into smooth spherocytes. Using the amphipath, lysophosphatidyl choline (LPC), as perturbant the discocyte-echinocyte-spherocyte transformation has been characterized in rabbit erythrocytes. Morphometric measurements indicate spherocytes possess 23% *less* surface area than disocytes. Removal of LPC results in a return to both discocytic shape and surface area. Such reversible changes may also be deduced from reversible increments in osmotic fragility that accompany the transformation in the absence of significant changes in cellular volume. In addition, no loss of any major lipid component accompanies the shape change. At the present time, none of the postulated mechanisms can account for the complexities of the complete transformation or the apparent but reversible loss of membrane surface area. It is suggested that the latter phenomenon may involve reversible changes in the packing densities of the components of the lipid bilayer.

(Supported by the President and Fellows of Middlebury College).

The Relationship of Cardiolipin Synthesis and Mg^{++} Concentration to the Membrane Stability of a Marine Bacterium

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A correlation between the requirement for additional Mg^{++} for growth and the absence of cardiolipin has been noted in several marine bacterial isolates. The possibility of a stability function for cardiolipin in membranes was examined in a non-fermentative marine isolate (MB41) which does not require added Mg^{++} but contains low levels of cardiolipin. This study was conducted to ascertain: (1) whether cardiolipin concentration varied when grown in the presence or absence of Mg^{++}, (2) whether cardiolipin synthetase activities were equal in those cells grown with and without Mg^{++}, and (3) if cardiolipin performs an osmostability function in cultures deprived of added $Mg.^{++}$ Radioisotope labeling during lipid synthesis, assaying for the specific activities of cardiolipin synthetase, and dilution-lysis experiments were performed. Results of these studies do not indicate an osmostability function for cardiolipin.

Characterization of Repetitive Sequences by High Resolution Direct-Derivative Melting of Calf Thymus DNA

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In contrast to published numerical methods, we obtain direct high resolution melting curves of DNA from the difference in absorbance between two identical solutions at a small constant temperature differential; monitored continuously with increasing temperature in a ratio recording spectrophotometer [Blake & Lefoley, *BBA 518:* 233 (1978)]. This method leads to significant enhancement of both sensitivity and resolution. As has been demonstrated [e.g., Vizard & Anseven, *Biophys. J.* 17:217a(1977); Mayfield, *BBA* 477:97 (1977)] eukaryotic DNA melting profiles show discrete subtransitions superimposed on a broad background; in patterns distinctive of the source. Using the bovine genome, we have established these subtransitions to represent repetitive sequence groups accounting for approximately 28% of the total DNA. The sequences in these repetitious groups appear to be simple, melting very sharply and within ranges of 2-4% G-C. Base compositions of these repetitive sequences were determined spectrally [Blake & Lefoley, (1978)] and quantitatively compare with reported values for satellite DNAs [Maio, *Hndbk of Biochem. and Mol. Biol. — Nucleic Acids*, v.II, p395, (1976)]. In melting curves of renatured DNA, the subtransitions corresponding to a given repeat group are characterized by lowered melting temperatures (Tm) and loss of resolution due to the increase breadths of the subtransitions. This can be interpreted as variability within a given repeat group of 3-6% based on the estimation that 1.5% mismatching lowers the Tm by 1°C [Laird et al, *Nature 224*:149 (1969)]. Such analysis lends itself to investigations of the rate of divergence between two DNS sequences. (MAES Project #8402; NIH, GM 22827)

Laboratory Scrutiny of Commonly Used Microvascular Clips

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The clips initially used for temporary occlusion in microsurgery were generally small neurosurgical aneurysm clips, and it is now widely appreciated that these clips cause significant endothelial damage when used even briefly on small vessels. Over the past five years, surgical supply houses have manufactured a variety of new clips, especially designed for temporary small vessel occlusion in the expanding field of microsurgery. We have studied this current generation of microclips from two stand points: first, the closing force developed by each clip was measured and compared to the theoretical minimum force required for occlusion. Secondly, these clips were used on rat carotid arteries which were then excised and opened longitudinally so that possible endothelial damage could be examined. Severe damage is produced in nearly all of the currently used microclips and only one design was found to be completely atraumatic by analysis with SEM.

Ovotransferrin Stimulates In Vitro Chick Erythroid Differentiation

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Clonal culture of erythroid cells from chick bone marrow in fibrin clots gave rise to spontaneous colonies, which although erythroid in morphology had little or no heme/hemoglobin. Addition of chicken plasma to these cultures stimulates heme and hemoglobin accumulation in the cells of the colonies. By fractionation of chick plasma and assay of the fractions for hemestimulating activity, a substance with a molecular weight of 80,000 and an isoelectric point of 5-6, was identified as the heme-stimulating serum factor. This substance may be serum transferrin. Ovotransferrin isolated from egg white also had heme-stimulating activity. Diferric-, monoferric- and apo- ovotransferrins were equally active. Ovotransferrin retains the heme-stimulating activity after isoelectrophocusing, electrophoresis, hydroxilapatite chromatography, partial trypsin digestion and fractionation by con-A Sepharose chromatography.

CLINICAL MICROBIOLOGY

Characteristics of Klebsiellae from Sewage Sludge and Composted Sewage Sludge

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While performing elevated temperature assays for fecal coliforms during a period lasting 18 months, high counts of fecal coliforms were observed in composted sewage sludge. Because values of greater than 2.4×10^5 fecals per gram were noted with some frequency by this method, tubes of EC broth that showed gas production at incubation temperatures of 44.5 degree C were plated on Levine's Eosin Methylene Blue agar and predominate cell types were identified by API 10 s strips, motility and antibiotic resistance. It was observed that 80 to 85% of cell types were of the genus *Kebsiellae.* In comparison to clinical isolates and *Klebsiella pneumoniae* ATCC 13883, the sludge derived isolates showed no difference in R_f values in analytical gel electrophoresis of bacterial DNA, standard biochemical tests as outlined by Edwards, metabolic activity measured by Warburg determinations of oxygen uptake, optimal and final pH curves, optimal temperature and survival capacity at extreme temperature ranges. It was concluded that there was no difference between the clinical and the sludge derived isolates in any test performed. It was noted that a rise of temperature above 44.5 degrees C improves the accuracy of the elevated temperature assay for fecal coliforms, i.e., *Escherichia coli.* Because of the high percentage of isolates of *Klebsiella* in composted sewage sludge, these compost piles may represent a reservoir of the genus *Klebsiellae* which may be spread to other environments and possibly man.

HUMAN GENETICS

Prenatal Detection and Management of Neural Tube Defects in Maine from a Consumer's Perspective: Results of a Survey of a High Risk Population

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In an effort to bring genetic services to Maine families at high risk for neural tube defects (NTD), the Meningomyelocele Project was incorporated as part of the statewide Genetic Disease Program in 1975. Services included genetic counseling, prenatal testing using amniotic fluid alpha-fetoprotein (AFP) determinations, and referral to appropriate management or support agencies, e.g., Meningomyelocele Clinic, Public Health Nursing, Maine Spina Bifida Assoc., etc. Questionnaires were sent to 62 parents of living children with meningomyelocele, 14 parents of deceased spina bifida children, 13 parents of babies born with anencephaly, and 4 adults with spina bifida in order to investigate the following areas as they related to the Meningomyelocele Project: involvement of Public Health Nursing, attitudes of physicians involved in treat-

ment and care, attitudes of educators, family and friends, financial burden associated with NTD, personal attitudes toward prenatal testing for themselves, their affected and unaffected children, and the low risk pregnant population. This paper will present the results of the questionnaire with specific emphasis on how prenatal diagnosis is viewed by different segments of this high risk population. Recommendations for improving delivery of services to NTD affected families are offered based on responses of survey participants.

Clinical Implications of Fragile Sites on Human Chromosomes

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Classical cytogenetic theory suggested that, in general, spontaneous or induced chromosome breaks occur randomly. However, recent data, made possible by the advent of banding techniques indicate that there are at least some chromosomal sites which are particularly susceptible to damage. These so called fragile sites appear as genetic traits which are inherited in a Mendelian fashion. They can be visualized as gaps, monochromatid or isochromatid breaks, acentric fragments, deletions or selectively endore-duplicated segments with break points always located at the same site in the same chromosome. We have recently observed a phenotypically normal male with a fragile site in the distal long arms of chromosome C-10 at band 10q24. Our particular concern in this case was the possibility of loss of the distal segment of chromosome 10 in gametic cells leading to partial monosomy in potential offspring. A review of the literature revealed that similar fragile sites have been observed in proximal 2q, 10q24, 16q22 and Xq26. With the exception of Xq26, no specific clinical correlations have been assigned to these fragile sites. The former has been associated with a sex-linked form of mental retardation. Partial monosomy or chromosome rearrangement involving the fragile site has not been observed in any of the offspring of carrier parents.

Trisomy 22 Variant (46,XY, + 22q-); A Case Study

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This is a case report of an 8-year-old male, first seen at our institution for evaluation of his learning disabilities. On examination he showed clinical findings consistent with Goldenhar's syndrome (oculo-auricular vertebral dysplasia OAVD). Because of his unusual facies, chromosome studies were requested. Trypsin-giemsa banding and quinicrine hydrochloride fluorescence staining of peripheral blood culture surprisingly revealed a variant of Trisomy 22 syndrome, Cat-eye syndrome (CES) (47,XY, + 22q-). The mother and one sib are normal phenotypically and have normal peripheral blood chromosome patterns. Although the reported cases of OAVD in which chromosome cultures were done have been reported as normal, many clinical features of OAVD and CES are quite similar and perhaps Goldenhar's syndrome might be another variant of trisomy 22. Cytogenetic examination might reveal either a mosaic pattern or some small chromosomal aberration. Clinical features and cytogenetics of a second case, an institutionalized 22-year-old female, diagnosed as having OAVD are compared with the index case. Chromosomes appear normal in both peripheral blood and skin fibroblast cultures. Physical anomalies are compared in a table. Although the etiology of OAVD remains uncertain, this study emphasizes the value of genetics as an aid in the differential diagnosis in complex clinical entities.

The Clinical Spectrum of Turner's Syndrome

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A 45 XO chromosome makeup confers on an individual the phenotypic picture described in 1938 by Turner, including female habitus and internal organs with streak, afollicular gonads, sexual infantilism, amenorrhea, short stature, wide (shield) breast, cubitus valgus, short neck, short digits and fourth metacarpals, and a high incidence of anomalies of the cardiovascular and urinary systems. Mosaic chromosomal patterns and patterns involving abnormal X chromosomes are associated with variations of this classical picture. A patient with 46 XXq-146 X del (X) (q12) had amenorrhea, sexual infantilism, shield breast, short stature, cubitus valgus, seizures and intellectual impairment. A patient with 45 XO and no sex chromatin in 200 cells of a buccal smear had stage III-IV breast development at 12 5/12 years, normal vagina with abundant secretions, FSH 12.4 mIu/ml and LH 4.5 mIu/ml. Palate was short and slightly high-arched, nipples slightly widely-spaced, and there was cubitus valgus, but only short stature was prominent. Another girl, 11 2/12 years, has stage IV breast development (with questionably widely-spaced nipples), normal menstrual periods for five months, short stature, short neck, high-arched palate, cubitus valgus, pigmented skin lesions, and a double right renal collecting system. These cases demonstrate the continuing impossibility of arriving at rigid correlations between peripheral blood chromosome morphology and phenotypes of patients with abnormalities of the X chromosome. Case 2 emphasizes the necessity of investigating the chromosomal constitution of phenotypic girls with significantly short stature even in the face of apparently normal pubertal development.

Development of a Paper Disc Technique to Measure Thyroxine Binding Globulin (TBG) in Newborns.

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The New England Regional Newborn Screening Program now tests all newborns for hypothyroidism by measuring T_4 in a filter paper blood sample. Up until now, the relationship between T_4 and TBG, its major binding protein, has been poorly understood in the newborn. The most crucial unsolved question involves the interpretation of low T_4 in premature infants. Is this due to low TBG or other factors, and when is it a real problem? Development of the paper disc TBG assay has been carried out as a first step in attempting to answer this.

Familial Hypophosphatemic (Vitamine D-resistant) Rickets: A Mouse Model

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Familial hypophosphatemic rickets (FHR) is a dominant X-linked, inherited metabolic disorder in man characterized by hypophosphatemia, decreased renal inorganic phosphate (Pi) reabsorption, osteomalacia, and frequent low serum calcium (Ca) with mildly elevated serum parathyroid hormone (PTH). Genetic and metabolic characteristics of the mouse mutation, hypophosphatemia *(Hyp)*, are sufficiently identical to those of FHR for the mutant mouse to serve as an animal model. Explanatory hypotheses are: 1) defective vitamin D metabolism, and 2) defective membrane transport of Pi. The defective vitamin D metabolism hypothesis was investigated by treatment of + /Y and *Hyp/Y* mice with 1α, 25-dihydroxyvitamin D_3 or its potent synthetic analogue, 1α-hydroxyvitamin D_3. Both metabolites corrected the hypocalcemia in Hyp/Y to levels at or moderately above those found in + /Y controls. High doses of both metabolites induced significant decline in excretion of Pi in both genotypes. 1α-hydroxyvitamin D_3, but not 1α-dihydroxyvitamin D_3, significantly elevated *Hyp/Y* serum Pi to levels equal to or greater than those of + /y controls. The results suggest that 1) renal Pi conservation in both genotypes follows suppression of PTH activity by vitamin-induced elevated serum Ca, 2) renal phosphate conservation alone does not correct the hypophosphatemia in Hyp/Y, and 3) hypophosphatemia in Hyp/Y can be repaired by 1α-hydroxyvitamin D_3. We conclude that the Pi transport system is functionally normal, if stimulated appropriately, and speculate that the primary genetic error leading to defective Pi transport could involve the vitamin D receptors or receptor blocking metabolites.

The Morphology of Amniotic Fluid Cells and Colonies in Culture

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We have attempted to distinguish the morphologies of amniotic

fluid cells in culture. Three basic morphological types have been suggested in the literature: (1) epithelial-like cells (E-type cells), (2) fibroblast-like cells (F-type cells), and (3) "amniotic fluid" cells (AF-type cells) (Hoehn et al, Pediat. Res 8: 746-54-1974). E-type cells are heterogeneous group with two to three morphological types predominating in this class. E-type cells are the predominant cell type in our cultures. The distinction between F-type and AF-type cells is subtle and presently can only be reliably distinguished by the types of colony they form. Our goal is to distinguish the various morphologies of cells in amniotic fluids and to determine if biochemical variations are reflected in the observed morphological variations. This information is important for the development of tests for prenatal diagnosis of biochemical disorders.

Breeding Community Formation in the Franco-American Population of Old Town, Maine

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The Franco-American community of Old Town, Maine and adjacent towns was formed by successive migrations from Canada and northern Maine beginning about 1840. Although the French census population was of substantial size from the beginning, the stable population was slow to form. This population process is described using record linkages of parish, civil, and census information. Problems in defining the spatial and temporal boundaries of this breeding population are discussed, as well as the implications for effective population size.

How Can We Determine Whether a Substance is a Human Mutagen?

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This century has seen an unparalleled rate of infusion of new chemicals and agents into the biosphere. This human-made infusion has already proved to have significant toxic effects on animals and plants and is seen to be a significant factor in human carcinogenesis. The most difficult aspect of human toxicity to measure is mutagenesis, for even with years of experience we still are unable to prove that any agent or chemical is mutagenic to humans in that it causes an increase in heritably transmitted mutations. But the proof of mutagenicity of human-used chemicals and agents on other mammals, plants, and microorganisms is clear. Humans do not provide the proof because they do not lend themselves to efficient rigorous experimental mutational analysis. The danger of undetected human mutagens in today's environment is to ourselves, our offspring and to distant generations. Therefore, there must be criteria established to evaluate and predict mutagen hazards for humans using studies other than those on transmissible mutations in humans. These criteria will include tests on human somatic cells, heritable mutation tests employing experimental animals and plants, and bacterial tests. This paper will be a discussion of the thinking of committees of the E.P.A. and N.I.H. recently established to prepare guidelines for mutagenicity monitoring and evaluation.

Pineland Center: Current Diagnoses and Evaluation

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Presented is an overview of a state institution for the mentally retarded. Out of a total population of 491, 292 males (59.5%) and 199 females (40.5%) ranging in age 7 to 76 years, more than 85% of all residents were found to be functioning in the severe to profound range of mental retardation, i.e., I.Q. below 40. The 10 most common diagnoses as outlined account for 85% of the total diagnoses. The diagnoses of perinatal hypoxia and/or mechanical injury at birth account for 11% (52). Chromosome abnormalities represent 8% (37) of which Down Syndrome was the most frequent with 31. All are trisomy-21 except for one case of mosaicism and one case of translocation. In comparing those with Down Syndrome, the male predominance persisted (31 males versus 9 females). The number of residents with inborn errors of metabolism was 3% (17), the majority due to PKU. The most common diagnosis (53% or 260) was retardation due to unknown prenatal influence. Clearly, continued research of these cases of unknown etiology must be continued. The significantly higher admission rate of male versus females is not clearly known. There are, however, no statistical differences between males and females when compared to age or degree of retardation. Also, there is no difference in the incidence of behavioral or seizure disorders between these groups. The metabolic screening tests are also discussed. The diagnoses of the outpatient evaluations are also presented.

Ascertainment of Newborn Cases of Down's Syndrome in Maine, 1976-1977

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Recent studies in Canada report that even though the number of older women bearing children each year has fallen dramatically, the incidence of Down's Syndrome has remained about the same instead of falling as expected. This could be due to better ascertainment or to unidentified environmental factors. In order to determine whether incidence is higher than expected in Maine, we attempted to ascertain all cases of Down's Syndrome born between Jan. 1, 1976 and May 31, 1977 by asking the voluntary cooperation of health professionals in Maine. Twenty confirmed or presumed cases of Down's Syndrome born during this period was ascertained. With an expected incidence of 18.9 cases and probable ascertainment deficiencies, it is possible that Maine has more Down's than expected, with Aroostook County having the highest rate—6 (1.8) expected). This study needs to be continued over the next 5 years in order to determine the significance of these observations. It is important for Maine to develop accurate ascertainment capabilities in order to develop and provide adequate medical and social services and to monitor genetic burden in our population.

Programming—The Bridge Between Research and Service

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The Maine Genetic Disease Program was established to provide genetic services to a rural population in an effort to reduce the burden of genetic disease in Maine. A description is presented of the methods and functions of the present Program, stressing the positive aspects of programming as a means to achieve our patient oriented goals. Problems in providing genetic services were encountered by each of Maine's specific disease project (Hemophilia, Down's Syndrome, Retinitis Pigmentosa, Neural Tube Defects). The solutions to these problems are presented as examples of the value of effective but flexible genetic disease programming. Advertisement and legislation are discussed as alternative methods to provide patient service resulting from genetic research. The advertisement approach is compared to an outreach approach. The Sickel Cell Anemia Screening Program is briefly described as an example of the problems encountered in mandating utilization of genetic research developments.

Proposed future activities of Maine's Genetic Disease Program will be discussed.

NUTRITION

Food Fortification

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Fortification, the addition of nutrition to food, is a widely used method for supplying populations in developing and industrialized countries with nutrients judged to be deficient in their food supplies. The attractiveness of fortification as a nutrient intervention policy is that it does not require changes in eating customs and therefore special education program. Obviously for fortification to be successful, accurate assessments of the nutritional needs of the populations involved must be available and the program must reach those most in need. In addition, there are a large number of technical and policy decisions which must be made for fortification programs to be successful. The complexity of these judgements will be discussed.

Nutrition and Mental Retardation

AGNES M. HUBER, Nutrition Department, Eunice Kennedy Shriver Center for Mental Retardation, Waltham, MA 02154

Two nutrition issues related to mental retardation will be discussed. 1) The first is concerned with the nutritional adequacy of the mentally retarded in institutions and community settings. Approximately fifty percent of the clients evaluated at the Shriver Center have nutrition related problems. These include obesity, poor food choices, a variety of feeding problems, problems related to seizure control medication and severe malnutrition due to rumination and other causes. Better qualified nutrition personnel is needed to deal adequately with such problems. With the recent tendency for deinstitutionalization and the care of the mentally retarded in the community, it will be necessary to develop community nutrition programs which will address these problems. Of particular concern are early intervention programs for pre-school developmentally delayed infants and children as well as setting nutrition standards for community residences for the retarded.

2) The second issue is concerned with the prevention of mental retardation and developmental delays by adequate nutrition during pregnancy and early childhood. Trace mental deficiencies of dietary origin or due to secondary causes have been linked to congenital malformations and developmental delays.

Nutritional Goals for the United States

JEAN MAYER, President, Tufts University, Medford, MA 02155

In the long term, our nutritional goal is simple, and attainable. It is a varied, acceptable, nutritionally-complete diet for every American. It was only ten years ago that we first recognized that there was widespread malnutrition in the United States. We have come a good distance since then in terms of poverty and consumer program, and have moved ahead to some extent in nutrition education and nutrition research. But we still have a way to go. We need to reexamine the effectiveness of programs already in place, and to improve on their scope and impact. We need better programs of nutrition education, for professionals as well as school children and the general public. We need to establish an ongoing system of nutritional surveillance that will help us to spot potential problems before they get out of hand. And we need much more research into the normal nutritional requirements of all age groups. Only such research can provide us with the knowledge of what constitutes a really good diet for optimal health and the prevention of disease and enable us to finally establish a rational food, agriculture, and nutrition policy for the nation.

The Performing Arts as a Medium for Nutrition Education

MARGARET E. BUTLER, University of Maine at Farmington, Farmington, ME 04938

With the combined guidance of the Franklin County Community Action Council, Inc., Rural Health Associates, the University of Maine and the schools of Franklin County, a pilot program of nutrition education was presented to all third graders in the county. The central figure was a performing artist "Franklin—The Good Food Friend," who presented regular nutrition shows in the classrooms with the help of teachers and nutritionists. Shows were planned to increase the children's awareness of the need to 1.) eat a variety of foods, especially fruits, vegetables, milk and foods high in iron; 2.) decrease food waste in school lunch; 3.) to improve snacking habits by decreasing concentrated sweets; and 4.) to become critical consumers. Several methods of evaluation were used including plate waste studies of all children who ate school lunch, twenty-four hour dietary recall of a random sample of children, parent and student questionnaires and anecdotal records. Specific suggestions are made for helping schools initiate this form of non-traditional nutrition education.

Prevalence of Overweight in Maine

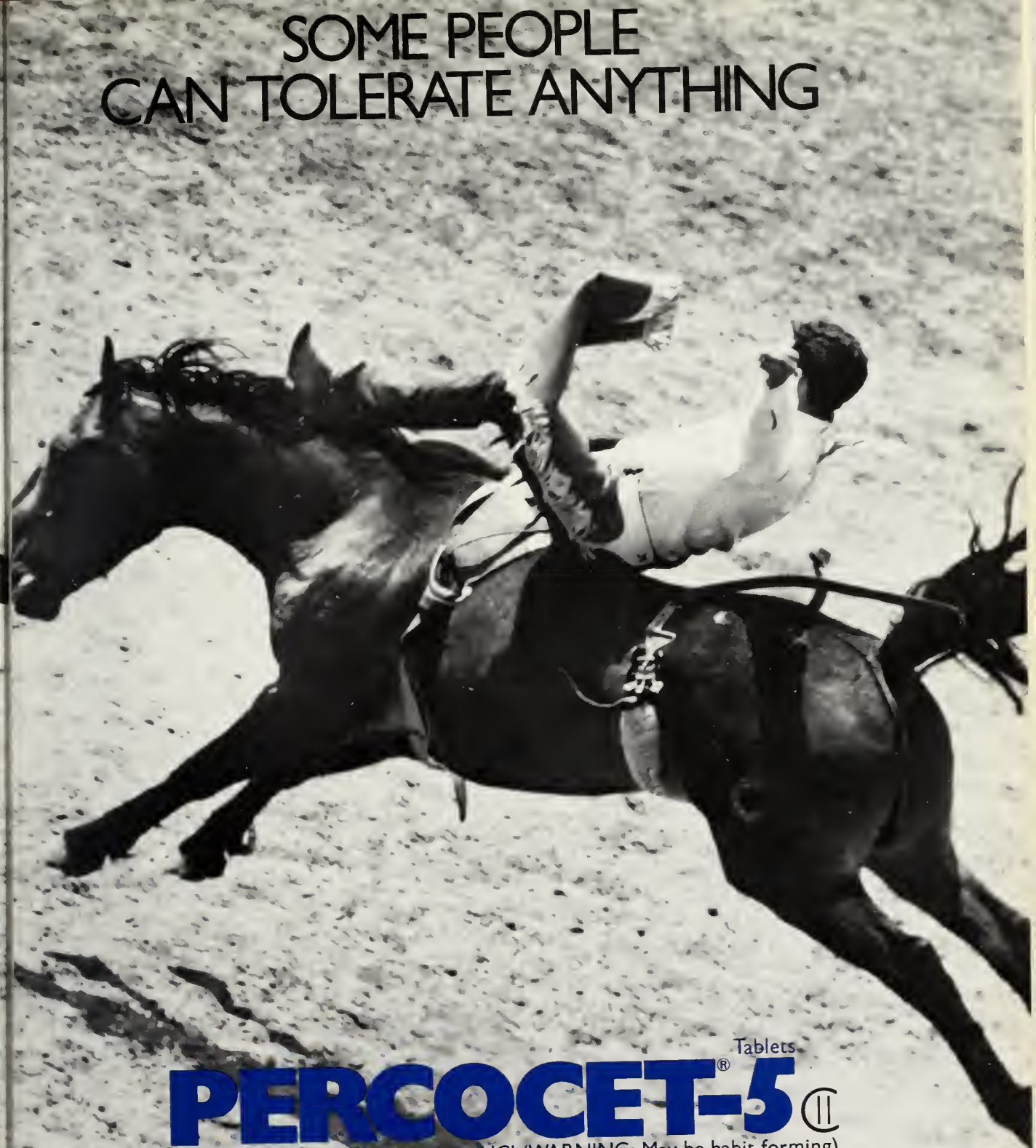
R.A. COOK, School of Human Development, University of Maine, Orono, ME 04473

Physical measurements were taken on 800 men and 800 women age 23-50. The sample population was obtained by selecting 50

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Tablets
PERCOCET®-5 (II)
Brief Summary of Prescribing Information
DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).
INDICATIONS For the relief of moderate to moderately severe pain.
CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.
WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.
Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.
Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.
Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.
Usage in children PERCOCET®-5 should not be administered to children.
PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.
Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.
Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.
ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.
Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.
DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.
DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS
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males and 50 females randomly from all 16 counties in the state. Measurements included height, weight, triceps skinfold, and midarm circumference. Weights were compared to average weight according to the National Health Survey 1960-1962 and to standard weight according to D.B. Jelliffe (World Health Organization, 1966). Mean heights of males and females were close to those of reference counterparts on which the recommended Daily Dietary Allowances are based, but weights of the Maine population were 24 pounds greater for males and 14 pounds greater for females. Fifty percent of the males and 35% of the females were above 110% standard weight, and 26% males and 22% females were above 110% average weight. Those in the weight range usually considered as obese (120% or more of standard weight) included 28% of the males and 21% of the females. When both sexes were combined, 42% of the population sampled was above 110% standard weight and 24% above average weight. Subjects in counties of high population density (urban, N = 500) were compared to those from other counties in the state (rural, N = 1100). Significantly higher weight, arm circumference, triceps skinfold, and fat area were found among the rural individuals, indicating larger weights due to fat.

Alternative Dietary Styles: Vegetarian Diets

J.T. DWYER, Frances Stern Nutrition Center and Tufts Medical School, Boston, MA 02111

Alternative dietary styles, including the use of health, natural or organic foods and vegetarian diets have lately become quite popular in young adults. Their offspring are often fed similar diets. For 3 years we have studied the diet, growth, and nutritional status of such persons and their children. While some vegetarians' diets fulfill the so-called dietary Goals and the Recommended Dietary Allowances for nutrients and are in good nutritional status others fail to meet the RDA and exhibit or report histories of various nutrition related problems. Finding among these two groups of subjects will be reviewed, with emphasis on the need for planning if certain types of vegetarian diets are to be used safely.

The Association of Obesity in Protein Malnutrition

V.E. JORDAN, Nutrition Consultant, Bureau of Health, Department of Human Services, Augusta, ME 04333

The well-nourished appearance of adults with excess body fat can obviate coexisting protein malnutrition. An evaluation of the nutritional status of 95 adults over 65 years old, living in central Maine, was made from anthropometric measurements of height, weight and thickness of the triceps skinfold; from biochemical analyses of blood and urine; and from data of dietary intake. Anthropometric measurements correlated with dietary energy sources but not with findings. In spite of sex related differences, thickness of the triceps skinfold correlated inversely with dietary energy sources and with age of the subject. The most significant value was obtained when protein intake was expressed as grams per kilogram body weight. Partial correlation analysis was used to investigate inter-relationships between skinfold thickness and dietary protein (grams per kilogram body weight) as influenced by other dietary energy sources. All partial correlation coefficients, even to the third order (adjusted for carbohydrate, fat and energy intake), were significant (P 0.001) and negative. None of the men had triceps skinfolds greater than 15 mm., the value for men selected to define obesity. The women were grouped into normal and obese (triceps skinfold greater than 25 mm.) and student's T-test was used to test for differences between the means for the parameters studied. The only significant difference between the normal and obese women was the mean values for protein intake per kilogram body weight. It would appear that protein intake may have a protective function against obesity.

Proposed Nutritional Basis for WIC Supplemental Food Package Modifications

P.J. KINCAID, Mid-Maine Medical Center, Waterville, ME 04901

The WIC Program Federal Regulations designate a maximum food supplement package for infants, women, and children. One of the criteria on which a person becomes eligible for this food supplement is nutritional need as specified by State Certification forms. The rationale for modification of this supplemental food package are: (a) Age groups with common nutritional problems and nutrition education needs can be given consistent support. (b) Nutritional supplements for different periods of growth, development or periods of stress would be consistent with educational goals. (c) Consideration of the Senate Select Committee's Dietary Goals for the U.S. implies modification in some cases. (d) Evaluation of the program is made a part of planning. (e) Effective and efficient use of program monies is increased through modification. The scope of this paper is a definition of the modification of this maximum food package that would be most nutritionally correct for the risk criteria identified. The modifications change the total quantity given, the calorie value or the nutrient concentration within a food package. Included are calculated %NRC-RDA for food packages as well as NCBR's for proposed packages.

The Effects of Protein Malnutrition on Recovery from Major Stress

W.E. JORDAN, JR., Chief of Surgery, Redington-Fairview General Hospital, Fairview Avenue, Skowhegan, ME 04976

Most major organ systems are thoroughly and knowledgeably studied prior to major surgery, but this is not usually done with the state of the patient's nutrition. We compared the morbidity and mortality of 100 elderly patients operated on consecutively at the Redington-Fairview General Hospital, in order to ascertain the effects of preoperative abnormalities on recovery. In this group, we found that a depressed serum albumin was the most serious preoperative laboratory value obtained. In a second group of 34 patients, selected because of their need for a standard, stressful procedure (colorectal cancer surgery), similar results were obtained. If the serum albumin was depressed the incidence of complications rose significantly. Other than factors concerning the disease itself and its spread, this was the most ominous preoperative laboratory value. At present, patients facing major surgery with serum albumin levels below 2.5 mgs. percent are receiving intensive preoperative nutritional therapy. If this succeeds in also reversing the increased morbidity and mortality, the case for nutritional repletion will be just as strong as for the correction of a diabetic imbalance, electrolyte depletion or renal failure and other, apparently more interesting, but no less vital, parameters.

Divergence of Food Intakes and Attitudes Among Vegetarians and Omnivores

LOUIS A.L. TABER, Research Nutritionist, University of Maine, Orono, ME 04473

Twenty-five male and 25 female adult omnivores and 25 male and 25 female adult lacto-ovo vegetarians between the ages of 20 and 50 years in Penobscot County were interviewed. Nineteen vegetarians also consumed fish on a regular basis. Their vegetarianism was a means of eating low on the food chain, thereby avoiding chemicals, additives, and processed foods, as well as denouncing American slaughtering practices. Anthropometric indices were similar between omnivores. Means for energy and nutrients, as determined by three day food records, were above 100% RDA for all groups, except for iron among female omnivores and vegetarians of 61% and 89% RDA, respectively, and energy of 90% RDA for female omnivores. Omnivores felt that the vegetarian diet was adequate nutritionally, provided proteins were complemented. Three male and two female omnivores rated their own intakes as bad. Four of these subjects had vitamin A below 66% RDA, one of whom had low intakes due to a self-imposed weight reduction diet. Three males and seven females, none of whom used supplements, indicated likely nutrient deficits. In two cases, iron and B vitamins were low, respectively. Eight additional females felt they had low intakes of nutrients found in vegetables. Iron intakes were consistently below 66% RDA, but nutrient deficits were offset by supplements in all except one case. Vegetarians were very outspoken in their negative criticism of the American eating style. Although only three vegetarians rated their own intakes as poor, 12 claimed nutrients deficits; only one subject, who did not use supplements, had nutrient intakes below 100% RDA. The other 11 had ample in-

takes, from 100% to 530% RDA for various nutrients.

Effect on Eating Patterns of a Special Supplemental Food Program for Women, Infants and Children

A.J. DERBYSHIRE and SUSAN DAVIS, Mid-Coast Human Resource Council and Pen Bay Medical Center, Rockland, Maine 04841

Clients for this program (WIC) are pregnant or post partum women, infants (1-12 mos.) and children under 5 years of age. Other criteria are a family income under 195% of poverty, and an unacceptable dietary pattern, or an abnormal anthropometric measurement, or a medical problem related to nutrition or a severe or chronic illness in the last year. Every month these clients are given vouchers for specific foods and are offered nutrition education. The foods so supplied include milk or cheese, eggs, fruit juice, and particular iron fortified cereals, and formula for infants. Only a few clients receive a modified food package. At each visit a recall is taken of the dietary intake for the last 24 hours. An analysis of these recalls gives evidence that WIC significantly increases the milk consumption in women, infants and children. In infants, consumption of vegetables is increased. In children, consumption of meat, vegetables and cereals is also increased. In women, consumption of fruits and milk is increased. In general, the variety of the diets of clients is less than in a control population. This study yields a preliminary description of the typical diet of this population sample of the mid-coastal area of Maine.

Nutritional Aspects of Iron Metabolism

H.N. MUNRO, Massachusetts Institute of Technology, Cambridge, MA 02139.

The body of an adult contains about 4 gm. iron, more as hemoglobin and in iron stores (1000 mg in male, 400 mg in female) as ferritin and hemosiderin. Factors regulating ferritin deposition and its function in iron storage have been extensively studied and will be discussed. Plasma ferritin levels reflect iron stores. The iron status of the body is regulated by absorption, which permits about 10% of dietary iron to be taken into the body. Although only about 1 mg. is absorbed daily, iron metabolism results in recycling of 35 mg. Fe daily. Iron-deficiency anemia is common, especially in pre-menopausal women. Deficiency occurs in three phases: loss of stores; fall in serum iron; deficient red cell formation. Recommended daily allowances for adults are 10 mg (men) and 18 mg (pre-menopausal women). However, mean intakes tend to be too low for women, especially during pregnancy. The provision of enough absorbed iron has been recently studied in relation to other constituents of the diet. It is now possible to calculate the proportion of iron available to the body on the basis of the amount of meat and of ascorbic acid in a meal. Examples of the effect of meal constituents on iron absorption will be given.

PULMONARY DISEASES

Pneumocystis Carinii Pneumonia

WILLIAM A. DEMICCO and JOHN S. URBANETTI, New England Medical Center Hospital, Boston and Mercy Hospital, Portland, ME

In this paper, we report a case of Pneumocystis carinii pneumonia in a monimmuno compromised host. The literature on Pneumocystis carinii in previously healthy patients is reviewed. The possibility of such infection in previously health patients, as well as the ever increasing numbers of immuno compromised patients in the community, makes Pneumocystis carinii a real diagnostic possibility in clinical community practice. The difficulties in diagnosing Pneumocystis carinii pneumonia, as well as the roentgenologic patterns, is also discussed.

The Relationship Between Right Duct Lymph Flow and Extravascular Lung Water in Dogs Given alpha-Naphthylthiourea

M.B. PINE and P.M. BEACH, Dept. Med., Col. Phys. & Surg., Columbia University, NYC

The relationship between right duct lymph flow and extravascular lung water was studied in 3 normal dogs and 15 dogs with pulmonary edema induced by alphanaphthylthiourea (ANTU). Right duct lymph was collected in a pouch created by ligating jugular, subclavian, and brachiocephalic veins. Extravascular lung water was measured in vivo by double indicator dilution and post-mortem by weighing lungs before and after drying. Cardiac output, pulmonary artery and pulmonary artery wedge pressures, and the concentration of protein and electrolytes in plasma and right duct lymph were determined. Eight lungs were examined by light and electron microscopy.

There was a direct relationship between right duct lymph flow and extravascular lung water. Dogs with severe ANTU-induced edema had extensive lung capillary endothelial destruction but only mild interstitial swelling and no visible damage to type I alveolar epithelial cells. Cardiac output, pulmonary artery and wedge pressures, and protein and electrolyte concentrations did not correlate with either extravascular water or right duct flow.

Thus, in ANTU-induced pulmonary edema right duct lymph flow was directly related to extravascular lung water with the highest flows occurring with severe edema. The absence of a rapid increase in lymph flow with small increases inextravascular water may be due to early sequestration of fluid in the alveolar space. Hemodynamic changes did not account for changes in lung water or lymph flow. The pulmonary interstitial factors relating increased extravascular water to lymph drainage remain to be determined.

Pulmonary Rehabilitation: Methods and Results at Eastern Maine Medical Center

A. MARSHALL SMITH, Respiratory Medicine Section, Eastern Maine Medical Center, Bangor, ME 04401

Pulmonary disability has become a major cause of lost time and wages, and an increasing cause for high medical expenses. Studies in various centers have shown a definite cost-benefit ratio to "Rehabilitation" programs. This paper will discuss methods of rehabilitation and outline the approach used at Eastern Maine Medical Center since the program was started in 1976. A summary of results will be given.

Pathogenesis and Clinical Management of Hyperuricemia and Gout

Richard J. Mangini, Pharm.D.

Abstract

Hyperuricemia and gout can either be primary disorders or secondary to other clinical conditions or drug therapy. In patients with primary hyperuricemia and gout, elevated uric acid levels are caused by increased production of uric acid, impaired renal clearance of uric acid, or a combination of both. Although the clinical expression of primary hyperuricemia and gout is probably genetically controlled, specific metabolic defects have been identified in only a small proportion of patients. Epidemiologic studies suggest that a number of environmental and social factors may contribute to the clinical manifestations of hyperuricemia and gout.

The clinical course of primary hyperuricemia and gout can be divided into three stages: (1) the asymptomatic stage, (2) the acute intermittent stage, and (3) the chronic stage. The main objective of treatment for all of these stages is prompt treatment and prevention of symptomatic gout, avoidance or reversal of any of the possible complications of hyperuricemia, and treatment of any associated conditions such as hypertension.

Treatment of an acute attack is directed at alleviating the patient's inflammation and pain with colchicine or other antiinflammatory drugs (phenylbutazone, oxyphenbutazone, indomethacin, etc.).

Indications for urate-lowering therapy (allopurinol or uricosuric agents) are: (1) frequent gouty attacks despite conservative treatment, (2) chronic joint changes with or without tophaceous deposits, (3) uric acid nephrolithiasis, (4) evidence of urate-induced renal damage, (5) uric acid serum concentration consistently above 9.0 mg/100 ml (non-automated colorimetric method), and (6) overproduction and hyperexcretion of uric acid.

> **"The victim goes to bed and sleeps in good health. About two o'clock in the morning he is awakened by a severe pain in the great toe; more rarely in the heel, ankle, or instep. The pain is like that of a dislocation, and yet the parts feel as if cold water were poured over them. Then follow chills and shivers and little fever. The pain, which was first moderate, becomes more intense. With its intensity the chills and shivers increase. After a time this comes to its height, accommodating itself to the bones and ligaments of the tarsus and metatarsus. Now it is a violent stretching and tearing of the ligaments, now it is a gnawing pain, and now a pressure and tightening. So exquisite and lively meanwhile is the feeling of the part affected that it cannot bear the weight of bedclothes nor the jar of a person walking in the room. The night is passed in torture, sleeplessness, and turning of the part affected and perpetual change of posture." Thomas Sydenham, 1683.[1]**

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The acute gouty attack and the crippling effects of chronic gouty arthritis were described as early as the fifth century B.C. However, it was not until the 19th century that elevated uric acid was demonstrated in gouty patients, and not until the 20th century that urate crystals were definitely implicated as the inciting cause of gout.

Uric Acid Production and Excretion

Uric acid is the end product of the metabolism of purines derived from both dietary sources and endogenous synthesis. Purines function as integral components of ribonucleic acid and high-energy phosphorylated compounds and are formed and degraded through a series of biochemical reactions (Figure 1). The immediate precursor of uric acid is xanthine; xanthine in turn is derived from hypoxanthine. Both reactions are catalyzed by the enzyme xanthine oxidase.[2-8]

Total body content of uric acid ranges from 1,000 to 1,200 mg in men, with a daily turnover of approximately 600 to 800 mg. The values are somewhat smaller in women. Of the daily turnover, approximately two-thirds is excreted by the kidneys. The remainder undergoes bacterial degradation in the gastrointestinal tract.[3,4,7] In severe renal failure, gut uricolysis plays a major role in uric acid elimination.[3] The mechanisms of renal clearance of uric acid are controversial and appear to involve a complex combination of glomerular filtration, tubular section and reabsorption.[2-4,7,9-12]

Uric acid is a weak acid with two dissociation constants (pK_a 5.7 and 10.3). At an acidic pH of 4.0 to 5.0, such as achieved in the urine, uric acid exists mainly as the poorly soluble free acid.[7,13,14] At physiologic pH, it exists primarily as the monosodium urate salt having an aqueous solubility of 6.4 to 6.8 mg/100 ml. In human plasma where a small portion of urate is bound to plasma proteins, primarily to an alpha 1-alpha 2 globulin, maximum solubility is 7.0 mg/100 ml.[7,13,14] However,

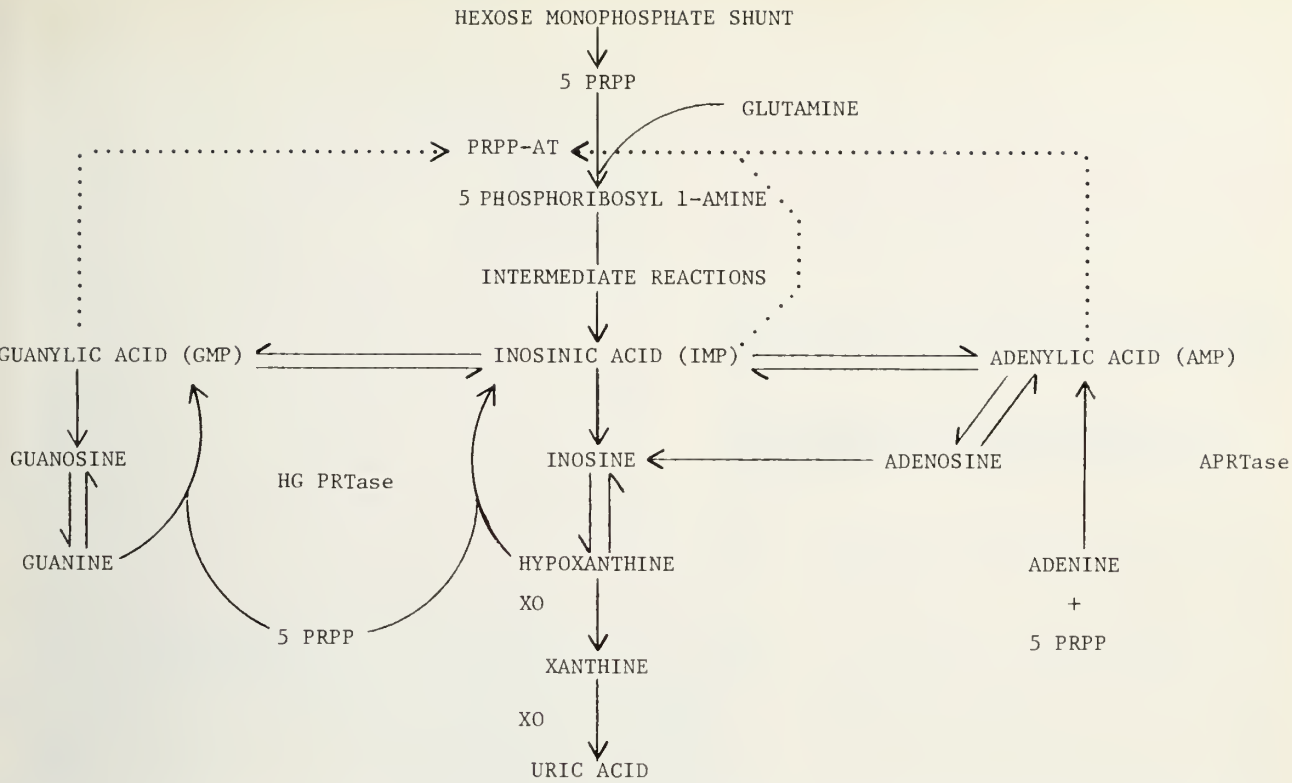


Fig. 1. Purine biosynthesis and degradation [key: 5PRPP = 5 phosphoribosyl pyrophosphate; PRPP-AT = phosphoribosyl pyrophosphate amidotransferase; HG PRTase = hypoxanthine-guanine phosphoribosyl transferase; ARPTase = adenine phosphoribosyl transferase; XO = xanthine oxidase]

monosodium urate can be held in solution in biologic fluids in appreciably higher concentration as the result of supersaturation. The cause of this as well as what mechanism ultimately provokes urate crystallization remains speculative.[15,16]

Epidemiology of Hyperuricemia and Gout

Hyperuricemia is a biochemical diagnosis and is defined as uric acid serum concentrations more than two standard deviations above the population "mean." The mean uric acid concentration depends on the sex of the patient and the particular analytic method.[8,14] The spectrophotometric uricase method is specific for uric acid and is not subject to drug interference. The upper limit of normal with this method (depending on the individual clinical laboratory) ranges from 6.5 to 7.5 mg/100 ml for men. Colorimetric methods for analyzing uric acid levels utilize reduction of phosphotungstate or other metal complexes. Colorimetric methods are nonspecific and can be falsely elevated by drugs.[17] The upper limit of normal in adult males for most non-automated colorimetric methods is 6.0 to 6.5 mg/100 ml and 7.5 to 8.4 mg/100 ml for the autoanalyzer (SMA 12/60) colorimetric method.[8,14]

For adult females the upper limit of normal is about 1 mg/100 ml less by each method. The estrogen-dependent sex difference becomes manifest at puberty and is related to a greater urate clearance in premenopausal women. The disparity diminishes or disappears when females reach menopause.[4,8,14,18]

The prevalence of gout in the United States is between 0.2 and 1.5% of the population. Asymptomatic hyperuricemia (i.e., elevated uric acid levels without clinical gout) occurs more frequently and is especially prevalent in relatives of gouty patients; in this group the incidence may be as high as 25%.[13,18-20]

Postpubertal men have higher uric acid serum concentrations than women, as well as a much higher prevalence of gout. Less than five percent of cases of primary gout occur in women, and these are mostly postmenopausal women.[13,19-21] However, recent evidence indicates that the incidence of gout in premenopausal women may be underestimated, particularly where there is a positive family history.[22]

Familial predisposition toward the development of gout has been recognized for centuries. Hyperuricemia and gout are polygenic in origin, with the clinical expression of the disease probably depending on the inherited genetic defect.[19,20] Social and environmental factors, including diet, obesity, and excessive alcohol intake, also appear to influence the overall incidence of hyperuricemia and gout.[18,20] Changes in environmental or social factors can unmask underlying genetic defects in uric acid metabolism and/or excretion.[18-20]

Hyperuricemia and gout also are commonly associated with clinical conditions such as hypertension, coronary heart disease, diabetes mellitus, and hyperlipoproteinemia. Although obesity has been suggested to be the common factor relating hyperuricemia and gout with these clinical conditions, cur-

rent evidence is inconclusive.[13,18-21,23] In the absence of these associated medical conditions, or end-organ complications of gout (i.e., nephropathy), patients with primary hyperuricemia and gout appear to have normal or near-normal life expectancies.[24]

Primary Hyperuricemia and Gout

In patients with primary hyperuricemia and gout, elevated uric acid levels are caused by increased production of uric acid, impaired renal clearance of uric acid, or a combination of both. A number of patients with primary hyperuricemia and gout overproduce uric acid. Although several inborn enzyme defects that increase uric acid production have been identified,[25-28] there are no identifiable enzyme defects in the majority of gouty patients. Patients who overproduce uric acid generally have an increased miscible urate pool (greater than 2.5 g) and frequently excrete excessive amounts of uric acid (greater than 600 mg/day on a purine restricted diet; 800 to 1000 mg/day on a normal diet). There is also a group of hyperuricemic patients in which the renal clearance of uric acid can be demonstrated to be significantly impaired. These patients generally have normal or near normal uric acid production with only a slight increase in the miscible urate pool. The overlap between these two types of gouty patients is considerable.[3,7,8,13,25]

Asymptomatic Hyperuricemia

Multiphasic screening procedures utilizing automated laboratory techniques have increased recognition of asymptomatic hyperuricemia. Between 20 to 25% of the relatives of gouty patients have elevated serum uric acid concentrations with no symptoms. Although as many as one-third of these patients may subsequently develop gout, the rest may remain asymptomatic for life.[13]

It is not possible to predict which patients with hyperuricemia will subsequently develop articular gout and its complications, and the need for treatment of the biochemical abnormality is not established.[29-32] Patients with asymptomatic hyperuricemia whose uric acid levels are less than 9.0 mg/100 ml by the colorimetric method (approximately 10.0 mg/100 ml by the uricase method and 11.0 mg/100 ml by the autoanalyzer method) probably do not require urate-lowering treatment, since the risk and cost of treatment may outweigh the potential benefit. These patients should be advised to maintain an ample urine output and to avoid high purine foods, and they should be checked at regular intervals for complications of hyperuricemia.[3,8,30-32] Weight reduction may be useful in those patients who are overweight.[30]

Based on the data that the incidence of gouty attacks and the development of its complications probably may be related to both the degree and duration of hyperuricemia, some authorities recommend urate-lowering therapy in patients with uric acid levels persistently greater than 9.0 mg/100 ml (colorimetric), particularly the overproducers/hyperexcretors of uric acid.[30,32] However, there is no definitive evidence that asymptomatic hyperuricemia by itself is harmful.[30] Thus, some recommend withholding urate-lowering treatment until articular gout or renal stones occur.[29] Treatment of associated conditions such as hypertension, diabetes mellitus, or coronary artery disease may be more important than direct reduction of uric acid.[30]

Acute Intermittent Arthritis

The acute gouty attack is characteristically of sudden onset with rapid development of swelling, warmth, and exquisite tenderness. Gout is mainly a disease of males, with the initial attack usually occurring after the third or fourth decade of life. Attacks occur primarily during the night or early morning and are commonly initiated by previous trauma, exposure to cold, or some dietary indiscretion. The first attack is usually unilateral and monoarticular. Any joint may be affected, but lower extremity joints, especially the big toe (termed podagra), are most common. The untreated attack will last from 3 to 14 days with eventual resolution and restoration of joint function. With repeated attacks the duration of inflammation increases as does the number of joints involved.[8,13]

Diagnosis of an Acute Gouty Attack

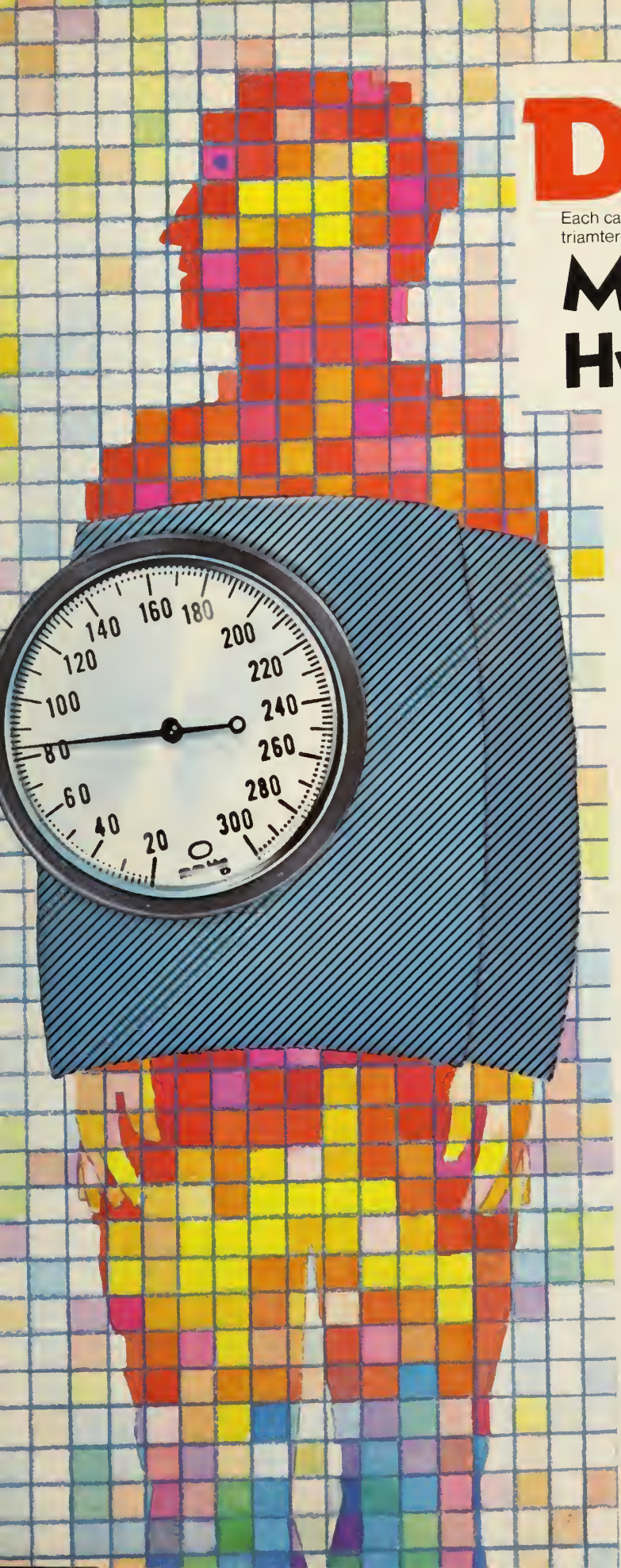
Diagnosis of an acute gouty attack may be established by identification of uric acid crystals in synovial fluid or a tophus.[13,16,21,33] However, in an occasional patient with gouty arthritis urate crystals may not be found due to difficulty in aspiration techniques, site selection and other physiologic factors.[33] Therefore, gout cannot be ruled out if the initial joint fluid analysis for urate crystals is negative. Alternatively, the presence of at least six of the following 12 criteria are considered diagnostic.[34] (a) maximum inflammation on one day only; (b) more than one attack; (c) monoarticular arthritis; (d) first instance of joint pain and swelling; (e) unilateral first joint pain; (f) unilateral tarsal pain; (g) redness; (h) suspect tophus; (i) asymmetric swelling; (j) subcortical renal cysts with no erosions; (k) no organisms can be cultured from joint aspirate; and (l) hyperuricemia.

Treatment of the Acute Gouty Attack

Treatment of the acute attack is aimed at alleviating pain and inflammation. The patient's activity should be restricted with immobilization of the affected joint. For the most effective response, antiinflammatory drug treatment should be started as soon as possible following the diagnosis of acute gout.[21]

Colchicine. Colchicine is the traditional drug of choice for the treatment of acute gout. The relative specificity of colchicine for gouty arthritis may be of diagnostic as well as therapeutic value.[8,35-38]

Continued on Page 122



Dyazide®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

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Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **Warning**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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When painful spasm
is the presenting
symptom...

...in the functional bowel/irritable bowel syndrome*

Bentyl®

(dicyclomine hydrochloride USP)

10 mg. capsules, 20 mg. tablets,
10 mg./5 ml. syrup, 10 mg./ml. injection

helps control abnormal motor activity
with minimal anticholinergic side effects†

Demonstrated smooth muscle relaxant activity.

In this double-blind study, twenty patients having G.I. series and exhibiting spasm were randomly selected to receive either 2 cc. of Bentyl or sodium chloride intramuscularly. Ten minutes after the injection another radiograph was taken . . .

. . . Bentyl produced definite relaxation in 8 of 10 patients. The sodium chloride produced relaxation in only 3 of 10. No side effects occurred in either group of patients.



Pylorospasm has almost totally blocked passage of barium meal.



Barium meal beginning to pass 10 minutes after intramuscular injection of 20 mg. Bentyl.

"The correlation of spasm relief and drug given was excellent."

*This drug has been classified "probably" effective in treating functional bowel/irritable bowel syndrome.

†See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964.

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8-4420 (Y736A) MNR-804

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(dicyclomine hydrochloride USP)

Capsules, Tablets, Syrup, Injection

AVAILABLE ONLY ON PRESCRIPTION

Brief Summary

INDICATIONS

Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the following indications as "probably" effective

For the treatment of functional bowel/irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis

THESE FUNCTIONAL DISORDERS ARE OFTEN RELIEVED BY VARYING COMBINATIONS OF SEDATIVE, REASSURANCE, PHYSICIAN INTEREST, AMELIORATION OF ENVIRONMENTAL FACTORS

For use in the treatment of infant colic (syrup).

Final classification of the less-than-effective indications requires further investigation

CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: Autonomic neuropathy. Hepatic or renal disease. Ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension. Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia, urinary hesitancy and retention; blurred vision and tachycardia, palpitations, mydriasis; cycloplegia, increased ocular tension; loss of taste, headache, nervousness, drowsiness, weakness; dizziness; insomnia, nausea; vomiting; impotence, suppression of lactation, constipation, bloated feeling, severe allergic reaction or drug idiosyncrasies including anaphylaxis, urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons, and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs.

Usual Dosage: Bentyl 10 mg. capsule and syrup: *Adults*: 1 or 2 capsules or teaspoonfuls syrup three or four times daily. *Children*: 1 capsule or teaspoonful syrup three or four times daily. *Infants*: ½ teaspoonful syrup three or four times daily. (May be diluted with equal volume of water.) Bentyl 20 mg.: *Adults*: 1 tablet three or four times daily. Bentyl Injection: *Adults*: 2 ml. (20 mg.) every four to six hours intramuscularly only. NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE: The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

Product Information as of October, 1978.

Injectable dosage forms manufactured by CONNAUGHT LABORATORIES, INC., Swiftwater, Pennsylvania 18370 or TAYLOR PHARMACAL COMPANY, Decatur, Illinois 62525 for MERRELL-NATIONAL LABORATORIES, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215, U.S.A.

However, colchicine also has beneficial effects in joint pain due to sarcoidosis and pseudogout, and in preventing attacks of Familial Mediterranean Fever.[35,37]

Impairment of leukocyte chemotaxis appears to be the principal mechanism of action of colchicine at usual therapeutic doses.[35,37,39,40] Recent evidence suggests that colchicine may also inhibit synovial phagocytic cells and tissue macrophages.[39,40]

Colchicine can be administered orally or parenterally and is a highly lipid-soluble drug with a short plasma half-life of about 1 hour.[35] Colchicine undergoes rapid cellular uptake, especially by the white blood cells where the drug is sequestered.[35,37,38] It is cleared partially by hepatic transformation and biliary secretion, as well as by renal excretion.[35,37,38] Measurable quantities of colchicine can be found in the urine for up to ten days after stopping therapy.[35]

Between 75 and 95% of patients with acute gout respond to colchicine.[8,21,35,37] The response rate depends on how promptly therapy is started. Colchicine is most effective when administered within the first twelve to 36 hours of the acute attack.[8,21,35,37,38] In situations where the start of treatment is delayed beyond this, indomethacin or phenylbutazone may be more effective.[21,36]

The dose of oral colchicine should be titrated to the patient's response and tolerance of adverse effects. For the initial attack, oral colchicine is given in doses of 0.5 to 0.6 mg every one to two hours until either joint pains are relieved, intolerable gastrointestinal symptoms occur, or a total dose of 6 to 8 mg is reached.[8,35,37] Joint pain and swelling should begin to subside within 12 to 24 hours after the initiation of colchicine. Complete relief may take one to three days. If necessary, the dosage may be repeated in several days or another antiinflammatory agent may be given.[21] Once the total oral dose of colchicine needed to control an attack is known, for subsequent attacks the patient should take half the total dose immediately and the rest in 0.5-mg doses at hourly intervals or as a single dose four to five hours later.[8,35,37]

Colchicine can also be administered parenterally. A single dose of 2 to 3 mg dissolved in 20 to 30 ml of normal saline given by slow intravenous injection is usually effective. An additional injection can be given after six to eight hours if necessary. No more than 6 mg should be given in a 24-hour period.[21,35,36,38] The intravenous route provides more rapid resolution of symptoms (four to twelve hours) and avoids most gastrointestinal toxicity.[8,35,38] Care must be taken to avoid extravasation because of the irritating nature of the parenteral solution.[21,35,36,38]

Colchicine toxicity is primarily gastrointestinal and includes nausea, vomiting, cramps, and diarrhea. Gastrointestinal toxicity is common, occurring in up to 80% of the patients receiving oral therapy.[8,35,41] Other adverse effects include alopecia, neurotoxicity, myopathy, transient bone marrow depression, and hepatotoxicity. These are primarily associated with

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excessive parenteral colchicine or reduced hepatic and/or renal clearance of colchicine.[36,37,41]

Other antiinflammatory drugs. Phenylbutazone, oxyphenbutazone, and indomethacin are useful alternatives to colchicine. An increasing number of clinicians prefer these drugs for treating an acute gouty attack, especially when the diagnosis is not in doubt.[21,26,42] These alternative drugs have the advantage of producing severe gastrointestinal toxicity less frequently than colchicine, while having equivalent therapeutic effectiveness.[8,21,26,36,42,43]

Phenylbutazone or oxyphenbutazone can be given in doses of 200 mg four times a day for one to two days, then tapering to 300 to 400 mg per day for an additional three to five days as inflammation subsides.[8,21,35,36,38,42,43] With indomethacin, 50 to 150 mg is recommended to initiate treatment, followed by 50 mg three to four times daily for the first day. This is tapered to 100 to 150 mg/day in divided doses for two to five additional days as inflammation resolves.[8,21,38,41] A schedule of 100 mg of indomethacin every four hours until relief, with tapering doses thereafter, has also been used successfully.[42] With either phenylbutazone or indomethacin, relief should be apparent within six to twenty-four hours. Complete resolution of inflammation usually takes three to five days.[42,43]

Sodium and fluid retention, as well as gastrointestinal complaints, are the most common adverse effects of phenylbutazone. Peptic ulceration has also been reported but is uncommon. Blood dyscrasias associated with phenylbutazone are rare with short-term therapy.[21,35,36,42]

Side effects may occur in 10 to 60% of indomethacin recipients, and include nausea, abdominal discomfort, dizziness, and headache.[35,38,42,43] The incidence of side effects depends on the dosage schedule; adverse reactions are more common in patients receiving more than 100 mg per day.[41] Some clinicians prefer not to use indomethacin because of the high incidence of side effects which can accompany its use.[35,38]

Fenoprofen, naproxen, and ibuprofen, recently marketed antiinflammatory drugs, also appear to be effective in relieving the inflammation of acute gout with minimal adverse reactions.[44-46]

Adrenocorticotrophic hormone (ACTH, corticotrophin) and corticosteroids may be used to treat acute gout but are primarily reserved for resistant cases (5%), especially those involving multiple joints.[21,26,36,38,42] ACTH in a dose of 60 to 80 units every six to eight hours for two to three days or prednisone 40 to 60 mg daily until relief is obtained are usually effective. Rebound of the attack may occur on steroid withdrawal. This can be prevented by tapering the steroids and giving colchicine prophylactically 0.6 mg, two to three times daily, during withdrawal.[42]

Interval treatment. After the initial attack of gout the interval between further attacks varies depending on the degree and duration of hyperuricemia. The patient may remain free from gouty attacks for a few days to several years or may even remain symptom-free. However, the interval between attacks generally decreases as the number of attacks increases.

The objective of therapy during this interval period is to reduce the number of acute gouty attacks and to prevent and/or ameliorate the complications of hyperuricemia. Treatment of those conditions associated with hyperuricemia and gout, such as hypertension, diabetes mellitus, and hypertriglyceridemia, is also important.[21]

Conservative treatment is indicated when uric acid levels are less than 9 mg/100 ml (colorimetric method), when tophaceous deposits, renal disease, or uric acid stones are absent, and when attacks are infrequent.[3,8,21] Conservative measures include dietary controls, weight reduction, adequate fluid intake, urinary alkalinization, and, in some cases, prophylactic antiinflammatory drug treatment.

Dietary control of purine intake will effectively decrease serum uric acid by approximately 1 mg/100 ml.[7] However, severe dietary restriction of purines usually is not tolerable to patients.[3,13,47] More realistically, patients should avoid high-purine foods (e.g., sweetbreads, anchovies, sardines, liver, kidney, and meat extracts) and any food known to provoke an acute attack. Excessive alcohol intake should also be discouraged.[21,23,48]

Weight reduction can be an effective means of lowering uric acid levels in the overweight gouty patient.[21,48] Weight loss should be gradual since crash diets can acutely raise serum uric acid.

The patient should also have adequate fluid intake (2 to 3 liters/day) and the urine should be alkalinized to prevent renal nephrolithiasis.[48]

Prophylactic colchicine is also useful in reducing the number of gouty attacks.[21] Daily administration of 0.5 to 1.5 mg of colchicine decreases the incidence of gouty attacks in as many as 75% of the patients.[21,26,38,49]

Indications for urate-lowering therapy. Indications for urate-lowering therapy are: (1) frequent gouty attacks despite conservative treatment; (2) chronic joint changes with or without tophaceous deposits; (3) uric acid nephrolithiasis; (4) evidence of urate-induced renal damage; (5) uric acid level above 9.0 mg/100 ml (colorimetric method); and (6) overproduction and hyperexcretion of uric acid. The aim of urate-lowering treatment is to maintain the serum urate level below 5.0 to 5.5 mg/100 ml (colorimetric method). Two groups of drugs are available to lower uric acid levels—uricosuric agents and the xanthine oxidase inhibitor, allopurinol. Drug selection depends primarily on the mechanism of hyperuricemia. In the overproducer/hyperexcretor, allopurinol is considered the drug of choice, while in the patient with normal renal function who excretes less than 600 mg/day of uric acid on a purine restricted diet either class of drugs may be used.[21] Urate-lowering therapy should not be initiated until after an acute gouty attack has completely subsided.[42]

Uricosuric agents. Until the development of allopurinol, uricosuric agents were the only drugs

available for lowering serum uric acid in hyperuricemic patients. Uricosuric drugs inhibit renal tubular reabsorption and increase the renal clearance of uric acid.[21,31,38,47,50-52]

The pharmacologic action of uricosurics is impaired in patients with renal insufficiency; increasing doses are required as renal function diminishes. When creatinine clearance falls below 25 ml/min, uricosurics are essentially ineffective regardless of the dose.[38,47] The activity of these drugs also is antagonized by concurrent administration of aspirin.[47,51,52] If a mild analgesic is required, acetaminophen or propoxyphene should be used. Drug intolerance, impaired renal function, and aspirin use are the most common causes of treatment failure.[47]

Reduction of serum uric acid by uricosurics decreases the number of gouty attacks and prevents further tophaceous deposits. Depending on the duration and effectiveness of treatment, preexisting tophi may be partially or completely reabsorbed.[21,47,51,53]

The uricosuric agent of choice is probenecid (Benemid®). It is well-absorbed from the gastrointestinal tract and is highly protein bound (90%). Probenecid undergoes hepatic metabolism to active hydroxylated and carboxylated metabolites, as well as inactive glucuronides.[47,52] The active parent compound has a six- to twelve-hour half-life. Probenecid and its metabolites are excreted by the kidney. Because probenecid is a weak acid, renal clearance can be markedly effected by urinary pH.[47,52,53]

The initial dose is 250 to 500 mg twice daily. The maintenance dose may be increased or decreased as required. Excessive dosing should be avoided at the start of therapy to prevent marked uricosuria and the possibility of uric acid stone formation.[36,47,53] Approximately 60% of patients will have adequate lowering of serum uric acid levels at a probenecid dose of 1.0 g per day.[53]

In patients allergic to probenecid, sulfinpyrazone (Anturane®) is an effective alternative. This sulfoxide derivative of phenylbutazone is rapidly absorbed by the oral route and is highly protein-bound. Its half-life is a relatively short three hours. Sulfinpyrazone undergoes hepatic metabolism to a parahydroxylated compound which is also active.[48,53]

The starting dose of sulfinpyrazone is 50 mg four times daily, with the average daily dose of 200 to 400 mg/day. In some cases up to 800 mg/day may be necessary. The initial dose should be low, for the same reasons as with probenecid.[36,47,53]

Stone formation is a major complication of uricosuric treatment. Nearly 10% of the patients treated with uricosurics may develop uric acid stones.[31,53] Patients should maintain a fluid intake of at least two to three liters a day. Alkalinization of the urine is indicated, especially during initiation of therapy.[21,47]

Uricosuric-induced exacerbation of gouty attacks occurs in the first few months of treatment in approximately 10 to 20% of patients.[31,38] Redistribution of tophaceous urate deposits or alterations in urate binding are possible mechanisms.[21,52] Colchicine in doses of 0.5 to 1.5 mg/day for the first six to twelve months of treatment is an effective and frequently used prophylactic measure.[47,53]

Other minor adverse reactions to probenecid include gastrointestinal irritation (8 to 18% of recipients) and hypersensitivity reactions such as fever and rash (5%). Probenecid appears to have no cumulative toxicity, and for this reason it is still preferred over allopurinol by many authorities in situations where either drug can be used.[47,53]

Gastrointestinal complaints and hypersensitivity reactions are the major side effects of sulfinpyrazone. Blood dyscrasias may be a rare complication. Sulfinpyrazone has antiplatelet activity and should be used with caution in patients with bleeding disorders or receiving anticoagulants.[31,52,53]

Allopurinol. Allopurinol (Zyloprim®) is the most effective drug available for lowering serum uric acid. Both allopurinol and its long-acting metabolite, oxipurinol, are xanthine oxidase inhibitors,[31,47,54,55] thus preventing formation of uric acid from xanthine. Inhibition of xanthine oxidase also reduces uric acid production by decreasing de novo purine synthesis; this is evident because of an overall reduction in the 24-hour excretion of uric acid, xanthine, and hypoxanthine.[47,54,55]

Allopurinol has a relatively short half-life of two to three hours, but it is largely converted to the long-acting metabolite oxipurinol (half-life 28 hours), which is slowly excreted by the kidney.[29,48,56]

Allopurinol is useful in treating all forms of hyperuricemia and is the drug of choice when (1) urinary uric acid exceeds 600 mg/day (purine restricted diet) where uricosurics may be hazardous because of the danger of uric acid stone formation, (2) there is a history of uric acid stones or calculi, and (3) hyperuricemia is due to or is complicated by renal insufficiency.[31,47]

The average daily dose of allopurinol is 300 mg, which can be given in divided doses or preferably as a single daily dose.[36,47,53,54] Reduction in serum uric acid is dose-dependent. A majority of patients will have a normalization of serum uric acid levels with a daily dose of 200 to 300 mg. Doses as high as 800 to 1000 mg a day may be required in resistant cases.[47,53] Lower doses should be given in renal failure since elimination of oxipurinol depends on renal clearance.

Following the initiation of allopurinol treatment, serum uric acid levels will generally begin to fall after one to two days, with maximal suppression in seven to 14 days.[47,53-55] The frequency of acute gouty attacks generally decreases within three to six months of allopurinol-induced normouricemia. Tophi, if present, begin to resolve in size by six months.[47,53-55]

Side effects are usually minor but may occasionally cause significant problems. As with uricosurics, initiation of treatment may induce exacerbations of acute gouty arthritis in approximately 10% of patients.[31,53] Prophylactic colchicine is frequently

recommended to prevent acute attacks during the first six to twelve months of treatment.[3,26,31,36,53] Gastrointestinal disturbances or minor skin rashes are common complaints in patients receiving allopurinol.[53] The most serious adverse reaction is a rare but severe allergic diathesis affecting multiple organ systems,[47,53] usually developing within the first six weeks of treatment. The syndrome is characterized by drug fever, eosinophilia, and maculopapular, pruritic rash which can progress to an exfoliative dermatitis or toxic epidermal necrolysis. Systemic complications include hepatomegaly, abnormal liver function tests or hepatic necrosis, as well as renal insufficiency and gastrointestinal bleeding. Several deaths have been reported. Concurrent thiazide diuretic administration and coexisting renal failure may predispose to this type of toxicity.[47] Other reported side effects include leukopenia (especially with cytotoxic drugs) and agranulocytosis, allergic granulomatous hepatitis, alopecia and ichthyosis.[47,53] A recent collaborative report indicates an increased incidence of rash in patients receiving both allopurinol and ampicillin (22.4%) in comparison with patients taking either ampicillin (7.5%) or allopurinol (2.1%) alone.[56] Renal stones or crystalluria comprised of either xanthine or oxipurinol are rare complications of allopurinol therapy that occur primarily in patients with excessive and/or uninhibitable overproduction of purines.[47,53]

A drug interaction of major clinical significance is the interaction of allopurinol with the thiopurines, azathioprine and 6-mercaptopurine. Thiopurines depend on xanthine oxidase for metabolism. Therefore their dosage must be reduced to one-third to one-fourth of the original dose to prevent severe thiopurine toxicity in patients also getting allopurinol.[47,55]

Chronic Tophaceous Gout

Chronic tophaceous gout is characterized by tophi—nodular deposits of monosodium urate that may be associated with a surrounding giant cell inflammatory reaction. The development of tophi depends on both the degree and duration of hyperuricemia. They usually do not form before the first gouty attack. Articular cartilage, synovium, renal interstitium, and other connective tissues are the principal sites of tophus formation. Affected joints become enlarged, stiff, and deformed, leading to chronic arthritis. Acute attacks may be superimposed on already chronically affected joints. These attacks occur more frequently, last longer, involve more joints, and are less amenable to treatment with standard antiinflammatory drugs.[13,21,57,58]

Uricosurics and/or allopurinol mobilize urates, decrease the size of or completely dissolve tophaceous deposits, and prevent further deposits.[13,21,59] Thus, since the advent of effective urate-lowering therapy, chronic tophaceous gout is seen less often. Chronic tophaceous gout previously occurred in approximately 50% of untreated gouty patients.[13,21,57]

Renal Complications of Gout

Acute tubular obstruction secondary to uric acid crystals is associated with greatly excessive uricosuria and usually occurs in patients with myeloproliferative or leukemic diseases undergoing cytotoxic treatment (see Secondary Hyperuricemia). However, patients with primary gout treated with uricosurics may on occasion develop obstruction, especially if they are overproducers/hyperexcretors of uric acid.[13,59,60] Acute obstruction is due to precipitation of uric acid crystals in the lumen of the renal collecting ducts, pelvis, and ureter. Depending on the severity of crystalluria, mechanical obstruction may occur; this can impede and ultimately completely block urine flow.[13,59,60] Renal failure is generally reversible. Treatment consists of lowering uric acid levels, alkalinization of the urine, and fluids and/or diuretics, depending on renal function. Hemodialysis may be required in some patients.[13,59,60]

A second renal complication of gout is uric acid nephrolithiasis. Between 10 and 25% of gouty patients develop uric acid renal stones; the frequency may reach 40 to 50% among overproducers/hyperexcretors of uric acid. The prevalence of uric acid stones depends on the plasma urate concentration as well as the level of urinary uric acid excretion. Abnormally acidic urine, apparently caused by defective ammonia production, has been found in some patients with primary gout. Since acidic urine favors precipitation of uric acid, this finding may contribute to the high incidence of uric acid stones in the gouty population.[13,60,61]

Stones are frequently the first indication of abnormal urate metabolism. Renal colic can be the first and sometimes the only symptom of hyperuricemia in up to 40% of patients who eventually develop primary gouty arthritis.[62]

Treatment and prevention of uric acid stones involve high fluid intake (two to three liters per day), alkalinization of the urine to a pH of 6.0 to 6.5, and allopurinol. Allopurinol decreases the amount of uric acid to be excreted by the kidneys and is the most effective drug in preventing recurrent uric acid stones. Moderate restriction of dietary purine intake is also advisable.[13,62,63]

Urate nephropathy is a potential renal complication of chronic gout. Between 15 and 20% of gouty patients have autopsy evidence of renal damage.[13,21,59-61] Histologic findings include deposition of monosodium urate in the renal medullary and pyramidal interstitium with surrounding giant cell inflammatory reaction. Nephrosclerosis and pyelonephritis are also commonly found, although other factors besides gout contribute to the frequency of these findings. The extent of urate deposition appears to correlate with the severity of gout.[58-61]

The clinical onset of urate nephropathy is gradual with limited reversibility, even with urate-lowering

Table 1

Drug-Induced Hyperuricemia[a]

Drugs	*Mechanisms*
Diuretic agents (except spironolactone)	Mechanism not fully-elucidated—volume depletion with increased proximal tubular reabsorption of uric acid and/or impaired tubular secretion
Alcohol	Lactic acid inhibits uric acid secretion
Aspirin	Low doses inhibit uric acid secretion
Cytotoxic drugs	Increases nucleic acid turnover and excretion
Ethambutol	Decreases uric acid renal clearance
Levodopa	Unknown
Nicotinic acid	Increases purine production; decreases uric acid excretion
Pyrazinamide	Inhibits uric acid secretion

a: Adapted from reference 3,20,30,64-66

therapy. Proteinuria and concentration defects are early signs. Progressive azotemia and hypertension may ensue, although mild proteinuria can persist for years without progression of renal impairment. Except on rare occasions, urate nephropathy does not precede the development of acute gouty arthritis. Thus, patients with symptomatic gout should have renal function tests regularly.[13,21,58-61]

Secondary Hyperuricemia

Hematologic diseases associated with hyperuricemia include several myeloproliferative disorders (such as polycythemia vera and myeloid metaplasia), certain hemolytic anemias and hemoglobinopathies, and, less frequently, leukemias.[20,21,28,64] In these cases secondary hyperuricemia is related to increased nucleic acid turnover and breakdown to uric acid. Serum concentrations in these patients frequently exceed 12 mg/100 ml. If they also receive cytotoxic drugs or radiotherapy, both of which enhance cell death and nucleic acid turnover, uric acid levels may become as high as 40 to 60 mg/100 ml.[28,64] Uric acid excretion is usually excessive, unless there is coexisting renal insufficiency.

Despite these exceedingly high urate levels, acute gouty attacks are relatively uncommon. When attacks do occur they can be atypical in character and resistant to standard treatments. Uric acid nephrolithiasis and rapidly-forming tophi occur more commonly than in primary gout and frequently antedate any acute attacks. Uric acid crystalluria and nephrolithiasis can lead to ureteral and/or tubular obstruction with acute renal failure.[64,65]

Allopurinol is the drug of choice and is indicated when uric acid excretion exceeds 600 mg/day (purine restricted diet) or serum uric acid is greater than 9.0 mg/100 ml. Allopurinol is not a substitute, however, for adequate hydration and urinary alkalinization.[13,20,30,32,64]

Hyperuricemia in patients with renal failure is secondary to reduced uric acid clearance. Uric acid serum levels usually begin to rise once creatinine clearance falls below 20 to 25 ml/min.[3,10,13,33] The incidence of acute gouty attacks in these patients is low (1%). Urate-lowering therapy (allopurinol) or prophylactic colchicine are usually not indicated in patients with diminished but stable renal function, since acute gout and urate stones are uncommon.

Certain drugs can elevate uric acid levels by increasing production and/or reducing excretion (Table 1). Diuretic-induced hyperuricemia is of some concern—more than 50% of patients with essential hypertension treated with diuretics may become hyperuricemic. However, most of these patients remain asymptomatic. Patients with a personal or family history of gout appear to be at greatest risk of developing gouty arthritis from hyperuricemia during diuretic therapy.[3,20,30,64-66]

Other secondary causes of hyperuricemia include lead poisoning, other neoplastic diseases, endocrine disorders (hypo- and hyperparathyroidism, Paget's disease), sarcoidosis, and psoriasis.

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Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The Maine Medical Association's House of Delegates, at its June 1976 meeting, adopted a regulation stating that a *minimum of 150* hours of continuing medical education is required in order to maintain membership. The policy took effect on January 1, 1977 and all members must be certified by January 1, 1980. Eligibility for certification begins January 1, 1977.

Credits required for the three-year period are as follows:

Category 1 — CME Activities with Accredited Sponsorship **(60 hours required)**	**No limit**
Category 2 — CME Activities with Non-accredited Sponsorship	**45 hours**
Category 3 — Medical Teaching	**45 hours**
Category 4 — Papers, Publications, Book and Exhibits	**40 hours**
Category 5 — Non-supervised individual CME Activities	**45 hours**
Category 6 — Other Meritorious Learning Experience	**45 hours**

Only active, dues-paying members are required to report. Please fill in your activity report promptly and return to the M.M.A. office, P. O. Box 250, Brunswick, Maine 04011.

LEGISLATIVE OUTLOOK

On January 3, the 109th Maine Legislature convened in Augusta. This opening session of the legislature, known as the First Regular Session, is expected to be very busy. As of the end of January, more than 2200 proposals, or bills, were awaiting the lawmakers' attention.

Undoubtedly, many of the bills to be processed will be about health care. Some of those will relate directly or indirectly to Blue Cross and Blue Shield of Maine and thus might require Plan action.

Described below are bills which we, at this point, are planning to support. All but the last one were submitted at our request.

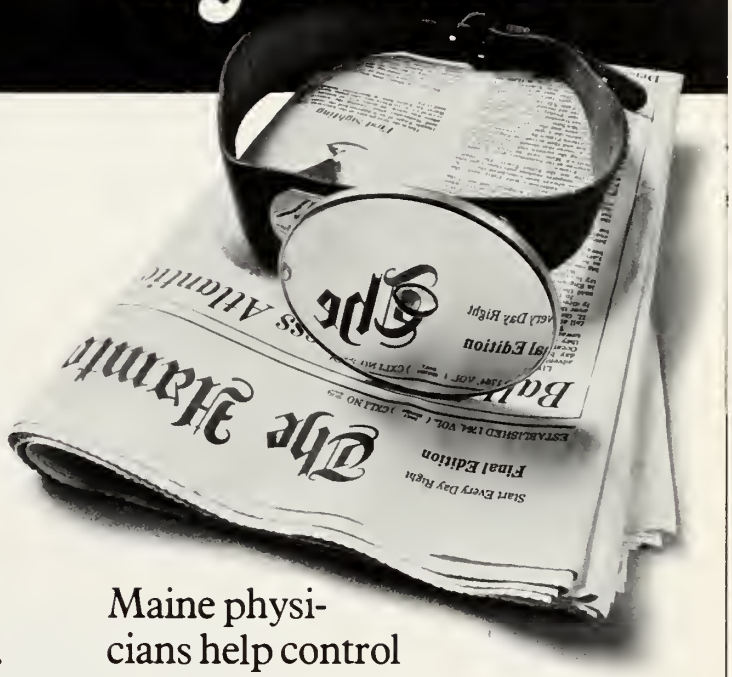
- A bill to amend the Health Facilities Information Disclosure Act to allow Blue Cross members to hold consumer positions on the Health Facilities Cost Review Board.
- A bill which would establish a patient "bill of rights", without adding to the cost of patient care.

Bills which we think we are going to oppose in the session include:

- A bill to mandate Blue Cross and Blue Shield coverage for mental health services.
- A bill to mandate Blue Cross and Blue Shield coverage of the treatment of alcoholism.
- A bill to mandate the coverage of Chiropractors' services.
- A bill requiring Blue Cross and Blue Shield to contract with all hospitals in good standing with the Department of Human Services. (This bill would be an attempt by Milo Community Hospital to resolve its long-standing disagreement with Blue Cross and Blue Shield.)
- A bill requiring Blue Cross and Blue Shield to pay a tax on premiums (i.e., subscription charges).
- A bill requiring Blue Cross and Blue Shield to pay a fee in lieu of real estate tax.

During the session, which could stretch into June or July, the list of bills of concern to us and our positions on bills will likely change. Some bills we have been expecting might not have been submitted or might eventually be withdrawn. On the other hand, there will probably be a number of bills which we have not anticipated. Then, too, bills can be revised and amended, sometimes so much so that we have to change our positions.

Ætna has good news for Maine Physicians.



Ætna Life & Casualty is expanding its Professional Liability Program in Maine. Currently, we insure over 300 Maine physicians and are pleased to be able to make this outstanding package available to more.

Put our experience to work for you. Ætna has instituted professional liability programs in many other states. One special feature is a cooperative program of Loss Control and Education. Where experience was favorable, Ætna was able to return premiums not needed to pay losses and expenses. We're now introducing this valuable feature in Maine.

By working with Ætna, Maine physicians help control the costs of their premiums by controlling their losses. At the same time receiving the necessary coverages required by today's medical realities.

All together, this adds up to good news for Maine physicians. For details, contact your local Ætna agent or return the coupon below.

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Without obligation, I'd like to know more about this Program.

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News, Notes and Announcements

Colby College
Waterville, Maine
1979 Summer Medical Seminars

Allergy and Immunology
16 hours—July 2-5
Director: Albert L. Sheffer, M.D.

Topics in Emergency Medicine
24 hours—July 8-12
Director: Earl Wilkins, M.D.

Epilepsy Course
18 hours—July 10-14
Director: Cesare T. Lombroso, M.D.

Topics in Pediatrics
17 hours—July 15-19
Director: Leo Stern, M.D.

Surgical Techniques
15 hours—July 17-20
Directors: John Reynolds, M.D. and Alfred Hurwitz, M.D.

Hematology
22 hours—July 22-26
Director: James R. McArthur, M.D.

Dermatology
16 hours—July 29-Aug. 2
Director: Wilma Bergfeld, M.D.

Neurosurgery
21 hours—July 22-26
Director: William Beecher Scoville, M.D.

F.T. Hill Otolaryngology Seminar
18 hours—July 29-Aug. 2
Director: Loring W. Pratt, M.D.

Ophthalmology
18 hours—Aug. 5-9
Director: Kevin Hill, M.D., F.A.C.A.

Nuclear Medicine
30 hours—Aug. 12-17
Director: Henry N. Wagner, Jr., M.D.

Obstetrics-Gynecology
18 hours—Aug. 12-16
Director: J. Donald Woodruff, M.D.

Forensic Medicine
21 hours—Aug. 19-23
Director: Michael M. Baden, M.D.

Pulmonary Disease
19 hours—Aug. 19-23
Director: Barry L. Fanburg, M.D.

Inquiries may be addressed to R.H. Kany, Director, Division of Special Programs, Colby College, Waterville, Maine 04901.

State of Maine
Department of Human Services
Division of Child Health Clinic Schedule—1979
By Appointment Only

Orthopedic Clinics

Bangor—St. Joseph Hospital
9:00 a.m.: Mar. 22, Apr. 26, May 24, June 28, July 19, Aug. 23, Sept. 27, Oct. 25, Nov. 15, Dec. 20

Fort Kent—Northern Maine Medical Center
9:00 a.m.: Mar. 13, May 15, July 10, Sept. 11, Nov. 6

Houlton—Houlton Regional Hospital
10:00 a.m.: Mar. 12, May 14, July 9, Sept. 10, Nov. 5

Presque Isle—A.R. Gould Memorial Hospital
9:00 a.m.: Mar. 14, May 16, July 11, Sept. 12, Nov. 7

Waterville—Mid-Maine Medical Center (Seton Unit)
Time scheduled by hospital: Mar. 5, Apr. 2, May 7, June 4, Sept. 10, Oct. 1, Nov. 5, Dec. 3

Cleft Palate Clinic

Portland—Maine Medical Center
9:00 a.m.: May 21, June 18, Sept. 17, Oct. 15, Nov. 19

Cardiac Clinics

Bangor—St. Joseph Hospital
9:00 a.m.: Mar. 9, Apr. 13, May 11, June 8, July 13, Aug. 10, Sept. 14, Oct. 12, Nov. 9, Dec. 14

Portland—Maine Medical Center
9:00 a.m.: Mar. 2, 9, 16, 23, 30, Apr. 6, 13, 20, 27, May 4, 11, 18, 25, June 1, 8, 15, 22, 29, July 6, 13, 20, 27, Aug. 3, 10, 17, 24, 31, Sept. 7, 14, 21, 28, Oct. 5, 12, 19, 26, Nov. 2, 9, 16, 30, Dec. 7, 14, 21, 28

Children's Development Clinic

Lewiston—Central Maine Medical Center
8:30 a.m.: Mar. 12, Apr. 9, May 14, June 11, July 9, Aug. 13, Sept. 10, Nov. 26, Dec. 10

National Conference on High Blood Pressure Control
April 4-6, 1979
The Washington Hilton, Washington, D.C.

A Major and Significant Conference on Controversies in Obstetrics

The Second Robert M. True Memorial Symposium

Presented by Family Physicians and Obstetricians of the State of Maine in cooperation with the Maine Fetal Risk Project and Mead-Johnson Laboratories.

APRIL 27, 1979, at the Red Coach Convention Center, 155 Riverside St., Portland, Maine.

Guest Speaker: Norman F. Gant, Professor and Chairman, Dept. of Obstetrics and Gynecology, Univ. of Texas Medical School, Dallas, Texas.

For information on registration call 1-800-492-0645.

Tufts University School of Medicine Announces Course

Tufts University School of Medicine announces "A Review of Recent Advances in Internal Medicine" to be held May 29-June 2, 1979, at the Boston Park Plaza Hotel, Boston, Massachusetts. The program is accredited by the AMA and the AAFP.

Further information may be obtained from the Office of Continuing Education, Box 36, 136 Harrison Avenue, Boston, Massachusetts 02111.

Board Certified Family Physician desires to do locum tenens for a two week period during the summer months in a small town preferably along the sea coast. Would also consider doing Emergency Room work if there was such a need.

Please send replies to
Benjamin G. Newman, M.D., F.A.A.F.P.
106 Boston Avenue
Altamonte Springs, Florida 32701

County Society Notes

Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges in Wiscasset on September 19, 1978.

Twenty-two members and five guests attended. The meeting was called to order by the President, Dr. Aldo F. Llorente; the minutes of the May meeting were read and accepted as read.

There was no old business.

Dr. David W. Schall presented the report of the Delegate: discussion of Blue Shield contract, purchase of parcel of land in Augusta for new Headquarters for M.M.A.

The Board of Censors recommended, and the membership approved, the elevation to active membership of Drs. Mark L. Dubay, Norman M. Rosenbaum and John S. Van Orden.

The Treasurer's report was read.

No action was taken on an AMA telegram regarding congressional efforts to revise Public Law 92-603, Section 227. No action was taken on the request by Dr. Melvin Bacon to sponsor a Diabetes Drive for Lincoln and Sagadahoc Counties.

The motion was made, seconded, and approved to endorse the M.M.A. Executive Committee resolution on Cost Containment.

No action was taken on the summary of S.3425 Community Mental Health Assistance Act.

There was no scientific program, and the meeting was adjourned.

FRANK O. AVANTAGGIO, JR., M.D., *Secretary pro tem*

Oxford

A regular meeting of the Oxford County Medical Society was held on October 11, 1978 at Positively Maine Street, South Paris, with fourteen members present.

The meeting was called to order by Dr. Kenneth G. Hamilton, President.

The reading of the previous minutes was dispensed with.

Position of the membership of one active member was reviewed and discussed.

A communication from the Chairman of the Diabetes Committee of the Maine Medical Association was read. It was decided that Rumford Community Hospital and Stephens Memorial Hospital can take part, if their medical staff so desires.

A Scientific Session was presented by two members of the Oxford Hills Internal Medicine Group. Dr. William L. Medd reviewed cases of rupture of the heart in acute myocardial infarction. Dr. Donald E. Ware discussed temporal arteritis and presented three case histories treated by his Group.

Nominating Committee Members who were appointed were: Drs. Stephen B. Dewing, David L. Phillips and H. Richard Bean. The Committee nominated the following officers for 1978-1979:

President: Dr. H. Richard Bean, Norway
Vice-President: Dr. Linwood M. Rowe, Rumford
Secretary-Treasurer: Dr. Harbans S. Sodhi, Norway
Delegates to the M.M.A. House of Delegates: Drs. Robert B. Funch and Michael A. LaCombe, both of Norway

Nominations were unanimously approved.

The Society members then adjourned for the social hour and dinner which was enjoyed by all.

HARBANS S. SODHI, M.D., *Secretary*

Penobscot

The first meeting of the 1978-1979 season of the Penobscot County Medical Society was held on October 17, 1978 at Pilots Grill, Bangor. Sixty-five members attended, including six guests of the Society: Dr. Leck, Dr. Hanley, Dr. Dowling, Dr. Morton and Dr. Maxwell. Mr. John Schroder of Johnson and Higgins Associates also attended.

The meeting was opened by the President, Dr. David S. Beebe,



Question: Which one of these professionals drives a leased car for $2.00 a day?

Answer: The one on the right. He's a doctor who leases a car from Lee Leasing and pays his own corporation $2.00 a day for his personal use of the car.
The rest of the lease payment is tax deductible. Would you like more details? Call Mike Allen. He'll be glad to supply them.

LEE LEASING

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and the minutes of the May 16, 1978 meeting were approved without addition or change. Following this, Dr. Maxwell presented information on the status of the Captive Insurance Company (Medical Mutual of Maine). There was a lively discussion of reasons for choosing Medical Mutual of Maine over the St. Paul and Aetna insurance companies. Drs. Hanley, Leck, Morton and Dowling participated in the presentation and fielded questions from the membership. Mr. Schroder further delineated the status of the new company and indicated that risks were being underwritten or reinsured by two of the largest insurance companies in the country. Dr. Hanley indicated that more than four hundred physicians have signed up and thereby affirmed the actions of the House of Delegates, which had instructed Maine Medical Association to investigate the development of a Captive Insurance Company in Maine.

Under new business, Dr. Beebe discussed the planned Medical Directory for Penobscot County and indicated that the final form which the Directory would take has not been decided upon yet. It was felt that a committee should be appointed to further investigate Cumberland County's experience with a directory in terms of cost, distribution, content and format. The matter of a surplus in the treasury was brought up by Dr. Thornton Merriam. Because of the proposed directory, increase in cost, and membership changes, it was felt that a reduction in the dues should not be considered at this time. Dr. Solomon has planned a treasurer's report for the November meeting. The feasibility of a County Medical Society listing in the yellow pages, enabling greater access to physicians who are still accepting new patients was discussed. Drs. Russell Lang and Marshall Smith contributed information in this regard. Further discussion concerning both the directory and the physician's listing in the yellow pages is planned for a future meeting when more information is available.

Six applications for full membership and six applications for junior membership were presented. All twelve applications were unanimously accepted. Those accepted into full membership were: Drs. Roe, Mainen, McPhail, Levy, McGill, and Allen. Those accepted as junior members were: Drs. Eaton, Holland, Newkirk, Goodwin, Himmelstein and Caine.

As it was getting quite late, our featured speaker, Dr. Kittredge made only brief remarks concerning cost containment and the future role of the Maine Medical Association and Penobscot County Medical Society in political action. There being no further business, the meeting was adjourned.

JAMES R. CURTIS, M.D., *Secretary*

Cumberland

The 424th meeting of the Cumberland County Medical Society was held on October 19, 1978 at Valle's Steak House. There were 104 members in attendance.

First readings for membership were given to Drs. James Maier and Eric Polk.

Unfinished Business:

Reports were given on Second Surgical Opinion Program, and on the Medical Mutual Insurance Company. Very few surgical second opinions have been sought, but a data gathering system will, nonetheless, go into effect so that the outcome of this program can be verified. There are now 425 physicians insured by the Medical Mutual Insurance Company within the State of Maine.

The retirement of Dr. George L. Maltby from active practice was recognized by a tribute from Dr. Robinson Bidwell and the presentation of a silver bowl to Dr. Maltby.

During the summer months, nine new members were inducted into the CCMS as follows: Drs. Alan Alexander, William Demicco, Joel Johnson, Barry Wood, John Barrett, David Ernst, Robert Sturges, Douglas Howell and Walter Allan.

New Business:

Resolutions were read on the deaths of Drs. Philip McCrum and Morrill Shapiro.

A ski trip to Switzerland, sponsored by the Cumberland County Medical Society, was described by Dr. Maxwell, and an update on the professional directory was provided.

The meeting adjourned at 8:45 p.m.

WESLEY J. ENGLISH, M.D., *Secretary*

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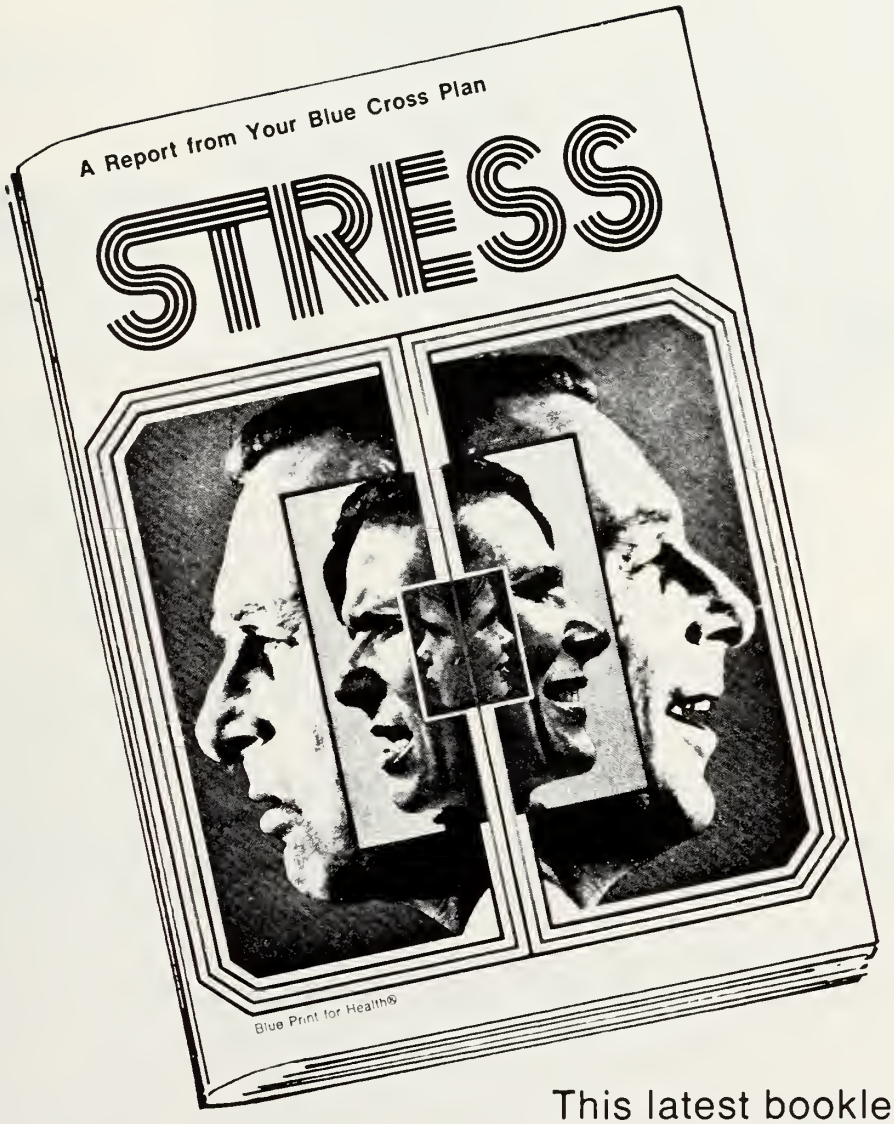
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A reminder

ZYLOPRIM®
(allopurinol)

100 and 300 mg scored Tablets

- inhibits uric acid formation
- helps prevent urate crystal depositions in synovia
- reduces risk of uric acid lithiasis

INDICATIONS AND USE: This is not an innocuous drug and strict attention should be given to the indications for its use. Pending further investigation, its use in other hyperuricemic states is not indicated at this time.

Zyloprim® (allopurinol) is intended for

1. treatment of gout, either primary, or secondary to the hyperuricemia associated with blood dyscrasias and their therapy;
2. treatment of primary or secondary uric acid nephropathy, with or without accompanying symptoms of gout;
3. treatment of patients with recurrent uric acid stone formation;
4. prophylactic treatment to prevent tissue urate deposition, renal calculi, or uric acid nephropathy in patients with leukemias, lymphomas and malignancies who are receiving cancer chemotherapy with its resultant elevating effect on serum uric acid levels.

CONTRAINDICATIONS: Use in children with the exception of those with hyperuricemia secondary to malignancy. The drug should not be employed in nursing mothers.

Patients who have developed a severe reaction to Zyloprim should not be restarted on the drug.

WARNINGS: ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme) and very rarely a generalized vasculitis which may lead to irreversible hepatotoxicity and death.

A few cases of reversible clinical hepatotoxicity have been noted and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. Accordingly, periodic liver function tests should be performed during the early stages of therapy, particularly in patients with pre-existing liver disease.

Patients should be alerted to the need for due precautions when engaging in activities where alertness is mandatory.

Nevertheless, iron salts should not be given simultaneously with Zyloprim. This drug should not be administered to immediate relatives of patients with idiopathic hemochromatosis.

In patients receiving Purinethol® (mercaptopurine) or Imuran® (azathioprine), the concomitant administration of 300-600 mg of Zyloprim per day will require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of Purinethol or Imuran should be made on the basis of therapeutic response and any toxic effects.

Usage in Pregnancy and Women of Childbearing Age. Zyloprim® (allopurinol) should be used in pregnant women or women of childbearing age only if the potential benefits to the patient are weighed against the possible risk to the fetus.

PRECAUTIONS: Some investigators have reported an increase in acute attacks of gout during the early stages of allopurinol administration, even when normal or subnormal serum uric acid levels have been attained.

It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. This interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

A fluid intake sufficient to yield a daily urinary output of at least 2 liters and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable to (1) avoid the theoretic possibility of formation of xanthine calculi under the influence of Zyloprim therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Patients with impaired renal function require less drug and should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in renal function appear.

In patients with severely impaired renal function, or decreased urate clearance, the half-life of oxipurinol in the plasma is greatly prolonged. Therefore, a dose of 100 mg per day or 300 mg twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels. Such patients should be treated with the lowest effective dose, in order to minimize side effects.

Mild reticulocytosis has appeared in some patients.

As with all new agents, periodic determination of liver and kidney function and complete blood counts should be performed especially during the first few months of therapy.

ADVERSE REACTIONS:

Dermatologic: Because in some instances skin rash has been followed by severe hypersensitivity reactions, it is recommended that therapy be discontinued at the first sign of rash or other adverse reaction (see WARNINGS). Skin rash, usually maculopapular, is the adverse reaction most commonly reported.

Exfoliative, urticarial and purpuric lesions, Stevens-Johnson syndrome (erythema multiforme) and toxic epidermal necrolysis have also been reported.

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In some patients with a rash, restarting Zyloprim (allopurinol) therapy at lower doses has been accomplished without untoward incident.

Gastrointestinal: Nausea, vomiting, diarrhea, and intermittent abdominal pain have been reported.

Vascular. There have been rare instances of a generalized hypersensitivity vasculitis or necrotizing angiitis which have led to irreversible hepatotoxicity and death.

Hematopoietic. Agranulocytosis, anemia, aplastic anemia, bone marrow depression, leukopenia, pancytopenia and thrombocytopenia have been reported in patients, most of whom received concomitant drugs with potential for causing these reactions. Zyloprim® (allopurinol) has been neither implicated nor excluded as a cause of these reactions.

Neurologic: There have been a few reports of peripheral neuritis occurring while patients were taking Zyloprim. Drowsiness has also been reported in a few patients.

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Drug Idiosyncrasy. Symptoms suggestive of drug idiosyncrasy have been reported in a few patients. This was characterized by fever, chills, leukopenia or leukocytosis, eosinophilia, arthralgias, skin rash, pruritus, nausea and vomiting.

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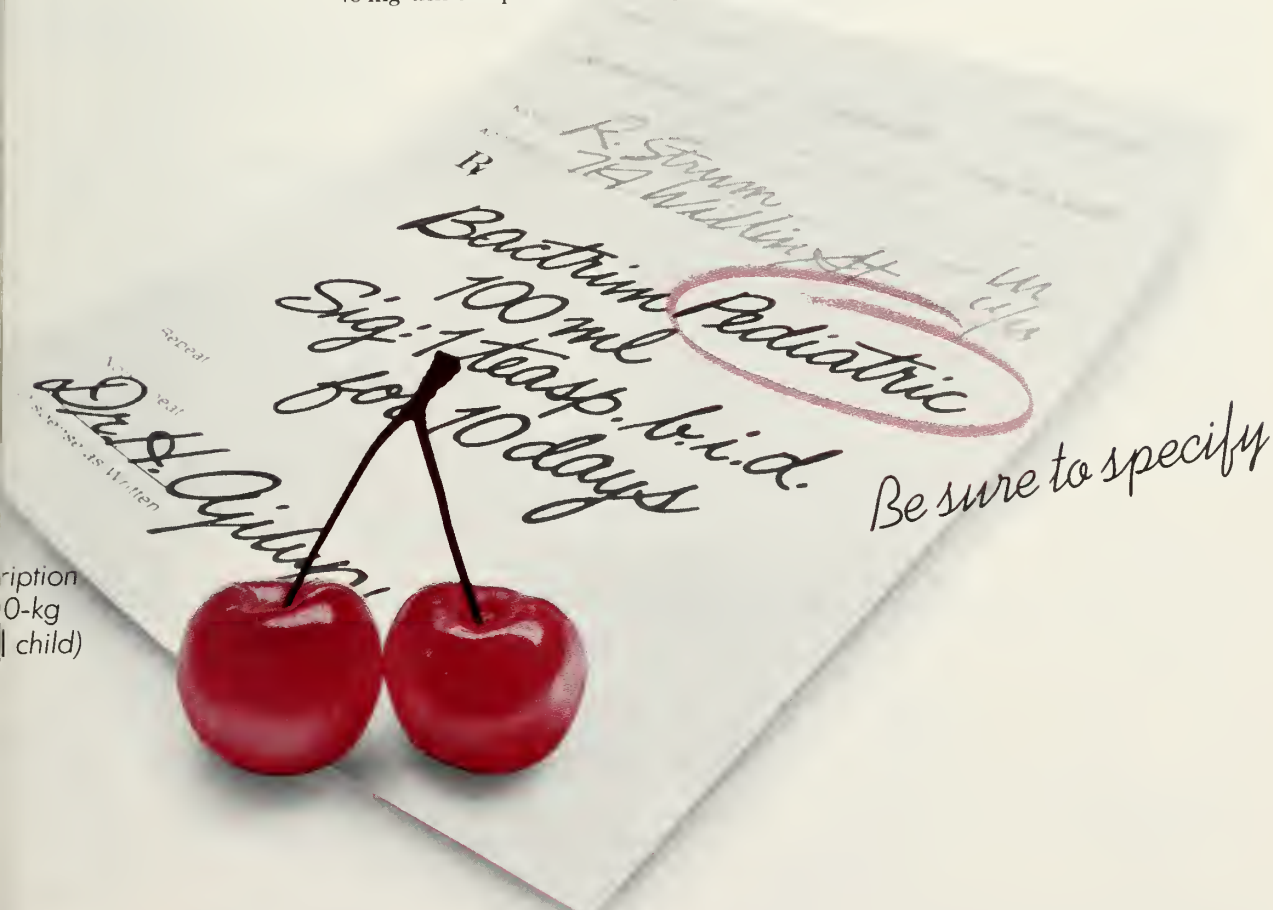
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Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

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The Journal
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Volume Seventy | Brunswick, Maine, April 1979 | Number 4

High Blood Pressure Control... The Maine Thing

N. Burgess Record, Jr., M.D., F.A.C.P.*

Introduction

Common, silent, dangerous, treatable, poorly controlled...these characteristics make high blood pressure (HBP) a major public health problem in developed nations around the world. Undetected and uncontrolled, hypertension threatens millions of Americans with early death and disability from cardiovascular disease. Detected and controlled, hypertension-induced stroke, heart and kidney failure can be prevented. Current national and state activity in hypertension control has prompted this update for physicians and other health professionals in Maine.

The National Scene

The Fourth National Conference on High Blood Pressure Control met in Los Angeles in April 1978. Abstracts from that meeting reveal several themes which deserve emphasis.[1]

High blood pressure (HBP) is more common than previously thought. Initial estimates (25 million Americans) included only people between the ages of 16 and 74. Disregarding age, 35 million people in this country have blood pressure greater than 160/95. An additional 25 million people have what is called "borderline hypertension" with pressures between 140-160/90-95.[2] Thus 70 million Americans, nearly ⅓ of the population, needs monitoring, risk factor modification and/or drug treatment.

Nevertheless, the national picture has brightened. Surveys reveal increased awareness, treatment, and control. In the 1960's and 1970's, the "rule of halves" prevailed. Of all hypertensives, half were detected; of those detected, half were treated; of those treated, half were controlled. This bleak situation has been replaced in the mid and late 1970's by the "rule of three-fourths." Nation-wide, 75% of all hypertensives have been detected; of those detected, 72% have been treated; and of those treated, 76% (among whites) have been controlled.[3] A marked increase in physician visits for hypertension between 1971 and 1976 reflects enhanced patient and physician attention to high blood pressure.

Initially, the national hypertension effort emphasized detection of unknown hypertensives. With a majority of hypertensives already identified, the need for mass screening may be less now than in the past. Nearly 90% of all Americans see a physician within a 2 year period. If all practicing physicians and other health care providers performed blood pressure measurements on a routine basis and referred or managed where appropriate, the need for screening would cease to exist. Nevertheless, hypertension screening remains useful in geographic regions not yet screened; in pockets of previously unscreened people, such as at industrial settings; and periodically in all communities to pick up those previously detected hypertensives who have "dropped-out."

Multiple and varied interventions seem to improve HBP control. Work-site blood pressure control programs, such as that instituted at Gimbel's Department Store in New York City, have achieved up to 85% control in their populations.[4] Occupational programs may be successful because they provide peer and social support, remove financial impediments to care, utilize a protocol-directed health care team and make health care convenient in both location and time. The New York program has demonstrated decreased absenteeism and cardiovascular morbidity in participating employees.

The financial cost for the program at Gimbel's has been offset by its financial benefits. Blue Cross-Blue Shield is currently studying the impact of work-site programs to determine actual cost-benefit ratios. Issues of confidentiality at the occupational setting seem not to be so crucial to employees as to health

*Rural Health Associates, Farmington, Maine 04938.

care professionals and have not been a major obstacle.

Blood pressure control in more traditional settings, including private practices, has been studied by the National Board of Medical Examiners.[5] In the practice setting, blood pressure control ranged from 17-86% with a mean of 56% control. At its best, private practice may offer as good a mechanism of blood pressure control as specialized control programs. Characteristics which identify those physicians who are able to attain such good control with their patients have yet to be determined.

Community-based hypertension programs have contributed to HBP control. The impact of community programs on vascular morbidity and mortality may be both prompt and substantial. In Milwaukee, Wisconsin, the death rate from cerebrovascular accidents dropped 38% (411 to 233 deaths) between 1974 and 1977, the interval spanning the life of the Milwaukee Blood Pressure Program. Similar, if not so dramatic, changes have been observed nation-wide. According to the National Center for Health Statistics, between 1970 and 1975 the United States experienced an extraordinary decrease in death rates from stroke (18%) and coronary heart disease (14%).[2] In all likelihood, diminished smoking and fat intake, improved exercise and blood pressure control have all contributed to this remarkable reversal of cardiovascular mortality.

Patient compliance remains a key element to HBP control. How to predict and how to improve compliance are less certain. Compliance is poor if patients perceive a long waiting time for care. Compliance improves when patients believe that HBP does and will effect their lives. Frequent patient-health professional contact seems to improve compliance and blood pressure control. The higher the blood pressure, the more the end organ damage and the greater "faith" in physicians, the better the compliance.

Despite the conventional wisdom that HBP is asymptomatic, 70-90% of patients with HBP say that they can tell when their blood pressure is up. They frequently associate headaches, dizziness and a sense of warmth with BP elevations. Paradoxically, those people who believe treatment of their blood pressure results in a decrease of the symptoms demonstrate increased compliance and increased control. Apparently patients expect to feel better when they are treated and feeling better improves compliance.[6]

Nationally, two groups coordinate hypertension control efforts. The National High Blood Pressure Education Program, supported by the National Institute of Health, continues to conduct major public education programs at the national level, and serves as a resource for state and community programs. Citizens for the Treatment of High Blood Pressure works for hypertension-related legislation, both at the national and state levels. Congress has recently authorized $25 million for fiscal year 1979, more than double the 1978 allocation of 314(d) funds for HBP activities in the 50 states. A federal austerity budget, however, may block distribution of the additional funds.

Many states have developed formal, coordinated hypertension detection and control programs. Some focus on education, others on screening, others on referral and follow-up and still others provide treatment programs as alternatives to conventional health care. Where state-wide programs are lacking, counties and regions within states have developed organized programs. New England, Massachusetts and Connecticut all have well-organized state programs. The Connecticut program features a state-wide computerized hypertension registry which has attracted considerable national attention and funding. A New Hampshire project demonstrated the efficacy of industrial screening in a rural state.[7] The New England High Blood Pressure Council has provided a regional forum and resource for the six state area.

A National Joint Committee representing major related health organizations (including the Academy of Family Practice, College of Cardiology, College of Physicians, Heart Association, Medical Association and the U.S. Public Health Service) recently reported guidelines for detection, evaluation and treatment of HBP.[8] The detailed report, which can be obtained from the Dept. of HEW, proposed six general guidelines:

1. Any group measuring blood pressure should have resources available for referral, confirmation, and follow-up.
2. Virtually all patients with a diastolic pressure of 105 mm. Hg or greater should be treated with antihypertensive drug therapy.
3. For persons with diastolic pressures of 90-104 mm. Hg, treatment should be individualized with consideration given to other risk factors.
4. The evaluation of patients with high blood pressure can be limited to a few baseline tests in most instances.
5. The stepped-care approach outlined in this report is advocated as a cost-effective method of treating most patients.
6. Treatment of patients with high blood pressure includes plans for facilitating long-term maintenance of blood pressure control.

The Maine Scene

Although much early work in HBP control involved southern and urban populations, Maine citizens have been increasingly involved in hypertension screening. Hospitals, home health agencies and civic/religious groups around the state have provided periodic blood pressure screening.[9] In 1974, Maine's Regional Medical Program provided funds to institute two separate blood pressure programs in the Augusta and Farmington areas.

The Capitol Region HBP Program in Augusta has conducted public or work-site screenings once or twice monthly since 1975. In 1977, 1500 state employees were screened. Three community clinics—

Winthrop, Augusta and Gardiner—provide regular interval blood pressure monitoring. Funded by the United Way and the Augusta General Hospital Associates, the Capitol Region Program has until recently been coordinated by Judith Feagin. The Augusta Program is one of few ongoing blood pressure screening programs which are successfully using volunteers to staff clinics on a continuing basis.[10]

Based in Farmington and coordinated by Jill Jasmin, the Franklin County High Blood Pressure Program is just concluding its fourth year of operation.[11] Endorsed by the medical staff of the Franklin County Memorial Hospital from the outset, the Program has become an integral part of hypertension management for both patients and physicians in West Central Maine. In four years, nearly 50% of the population over age 12 has been screened. The total number of identified "actual" hypertensives (untreated, treated, and treated-controlled) numbered 2,782 people as of July 1977. Over a 3-year period, the proportion of treated hypertensives rose from 53% to 68% and those well-controlled from 21% to 43%. More frequent routine BP checks in physicians' offices has been documented.[12]

The Franklin County Program emphasizes public, patient and provider education; frequent interval blood pressure checks and counselling at regularly scheduled blood pressure centers in each of 12 communities; and encouragement of a "therapeutic alliance" between patient, private physician and blood pressure nurse. The Franklin County Program has supplemented and complemented rather than competed with the traditional physician-patient relationship. This may be one major reason for its success.

Program funding has come variably from Regional Medical Program; 314(d) money from the State Department of Human Services; and a HURA (Health Underserved Rural Area) grant. Increasingly, the Program has looked to financial support from patients, initially in the form of 50¢ donations and most recently as professional fees of 50¢—$1.00 per visit. The Program will soon explore the role of third party payors in out-patient blood pressure control.

Other programs have developed throughout the state. Some have adapted the Franklin County model to their own circumstances; others have devised new approaches. Of particular interest is a combined industrial screening and education project conducted in March 1978, at the Hathaway Shirt Factory in Waterville. Staff from the RISE (Regional In-Service Education) Project of the Kennebec Valley Regional Health Agency screened 272 employees.[13] Special counselling and educational sessions were offered to employees with uncontrolled HBP. Area physicians participated in program design and, in general, encouraged patient participation in the educational program.

Within the last two years, the Division of Public Health Nursing has emphasized hypertension screening and follow-up as part of a more comprehensive Adult Health Assessment Program. The Department of Human Services recently entered into a contractual relationship with twelve area health agencies using 314(d) funds to provide partial compensation for high blood pressure detection and control activities. These agencies include: Community Health Service—Portland; York County Health Service—Saco; Androscoggin Home Health Services—Auburn; West Central Maine Health Services—Farmington; Bath-Brunswick Regional Health Agency—Bath; Kno-Wal-Lin Community Health Agency—Rockland; Penquis CAP—Bangor; Four Town Nursing Service—Bluehill; Aroostook Regional Task Force on Aging—Presque Isle; Kennebec Valley Regional Health Agency—Waterville; Kennebunk Public Health Association—Kennebunk; and Bangor Health Department—Bangor.

Table 1

Age Specific HBP Criteria

Age	*Systolic*	*Diastolic*
3-5	110	70
6-12	130	80
13-20	140	85
21-40	140	90
41-60	150	90
61-80	160	95
over 80	170	95

Although covering less than half the cost of HBP control programs, such compensation will facilitate continuing attention to the problems of hypertension control in the state. Depending on federal legislation, funds available for this use in future years will vary. Much more funding will be needed to do an adequate job everywhere in the state.

Unlike Georgia, where direct patient care and medication are provided by county and state blood pressure programs, no HBP program in Maine provides direct patient care. As the result, the cost of medical care and medication may remain a burden for certain segments of the population. Emphasizing cardiovascular medication, Maine's Drugs for the Elderly Program does lower financial barriers to control for some senior citizens. Fortunately, when studied carefully, the cost of medication is usually not a major obstacle to control.

During the first 6 months of 1978, a Maine High Blood Pressure Council has taken embryonic form under the direction of Dr. George Pauk. This Council now includes representatives of the Maine Heart Association, Maine Medical Association, Maine Osteopathic Association, Medical Care Development, State Department of Health and the Health Education Resource Center of the University of Maine, Farmington. Council task forces are working on a state plan for blood pressure control, state-wide standards, patient and professional education, and occupational control. The standards committee has recently recommended age-specific BP screening criteria (see Table 1). Confirmed elevations of either

systolic or diastolic pressure would call for referral for medical evaluation.

The Council hopes to promote hypertension activities in Maine, to serve as a resource to professional and community groups and to coordinate efforts to attract additional sources of funding for hypertension activities in Maine.

Summary

As much as anywhere in the United States, hypertension poses a major public health problem for the people of Maine. High blood pressure is common in Maine. The barriers which hinder detection and control in a predominantly rural state can be overcome in part by multifaceted regional programs. Interested agencies and individuals throughout the state have begun a dialogue—the HBP Council—from which may evolve a coordinated approach to controlling this major risk factor.

The patient-doctor relationship holds a high place in the esteem of Maine people. Efforts to reduce the high cardiovascular and cerebrovascular toll of hypertension should focus on the strength of this relationship, and should seek ways to help patients and their physicians work together for improved blood pressure detection and control.

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Reference:
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Dupuytren's Contracture as a Cause of Stenosing Tenosynovitis

HOWARD G. PARKER, M.D.*

ABSTRACT

Five patients with Dupuytren's contracture causing a painful nodule at the distal palmar crease, involvement of the A-1 flexor pulley, and secondary stenosing tenosynovitis are reported. All patients were referred for management of painful trigger fingers. In each instance the referring physician overlooked the presence of Dupuytren's contracture.

Dupuytren's contracture usually involves the pretendinous or longitudinal fibers of the palmar fascia over the fourth and fifth metacarpophalangeal joints and the ring and little fingers (Figs. 1 and 2). Occasionally it involves other metacarpophalangeal joints, fingers, and thumb. Caucasian men, fifty years of age or older, are most commonly affected. The condition usually starts with a small nodule at the distal palmar crease; gradually, other nodules appear, lessen in size, and seem to coalesce into continuous tight bands. Tenderness is unusual, and triggering or locking of the fingers is rarely reported.[2-5]

Stenosing tenosynovitis, or trigger finger, is a constrictive state involving the flexor tendons at the level of the A-1 pulley[1] over the metacarpophalangeal joint. Usually it occurs spontaneously in middle-aged women. The pulley gradually becomes thicker and narrower with age, and the flexor tendons hypertrophy in response to increased impingement within the pulley. Localized swelling or cicatricial formation within the tendon may occur. The thickened area may become trapped proximal to the pulley causing a block to extension of the flexed digit or distal to the pulley causing a block to flexion of the extended digit. Patients complain of pain in the proximal interphalangeal joint and in the region of the distal palmar crease.[3]

MATERIALS AND METHODS

Three women and two men whose ages ranged from fifty-eight to seventy-six years were referred with the diagnosis of trigger finger (Table 1). Four patients had painful locking in flexion of the ring finger, and one patient had involvement of the little and middle fingers. All complained of pain in the dorsum of the proximal interphalangeal joint, especially when the finger was locked. Locking occurred in flexion in all patients and was most frequent in the morning upon arising and after repetitive chores, such as sewing or pruning bushes. Duration of symptoms varied from six months to two years. None of the patients were alcoholics and none had epilepsy or diabetes. Results of laboratory tests, including the sedimentation rate, latex fixation test, uric acid, glucose tolerance test, and liver function studies, were negative or within normal limits in all patients.

A large subcutaneous nodule or thickening of the palmar fascia was found at the level of the distal palmar crease in each patient. None of the patients had flexion contractures of the digits. In three patients similar nodules were seen near the distal palmar crease in one or more adjacent rays. No neurovascular abnormalities were observed.

All patients were operated on. Regional anesthesia (axillary or vein block) was used, and a tourniquet was applied after exsanquination of the hand and forearm with a rubber bandage. A zigzag volar approach over the involved region was employed. In each patient the thickened area noted before operation turned out to be a portion of the longitudinal or pretendinous fibers of the palmar fascia. The transverse fibers were loose and appeared normal. Vertical longitudinal fibers extending toward the metacarpophalangeal joint and those in the region of the A-1 pulley were intimately involved or attached to the volar aspect and sides of the A-1 pulley.

It was difficult to distinguish palmar fascia from the pulley. When the involved finger was passively flexed, the tendons did not move proximal to the pulley until gentle traction was applied with a small, blunt hook. The tendons were then blocked proximal to the pulley by a small, thickened mass within their substance and only by extending the digit passively could the tendon be returned through the pulley.

A subtotal fasciectomy was performed and included all of the palmar nodule, most of the pretendinous band proximal and distal to the nodule, and the vertical fibers and volar portion of the pulley. In every instance the neurovascular structures adhered tightly to the thickened fascia in the region of the pulley and required careful dissection and identification before fasciectomy.

RESULTS

All patients had follow-up studies for a year or more after operation. Locking did not recur. In one patient nodular thickening of the palmar fascia recurred about six months later, but no locking or triggering occurred and no further operation was performed. Bowstringing of flexor tendons did not occur in any patient.

COMMENT

All five patients had concomitant palmar fascia contracture and stenosing tenosynovitis. Extension of

*Reprint requests to Department of Orthopaedic Surgery, 65 West Main St., Dover-Foxcroft, Maine 04426.



Fig. 1. A, A sixty-year-old man with typical appearance of Dupuytren's contracture along the fourth metacarpal phalangeal joint. B, Same patient showing the position of locking when the ring finger was flexed.

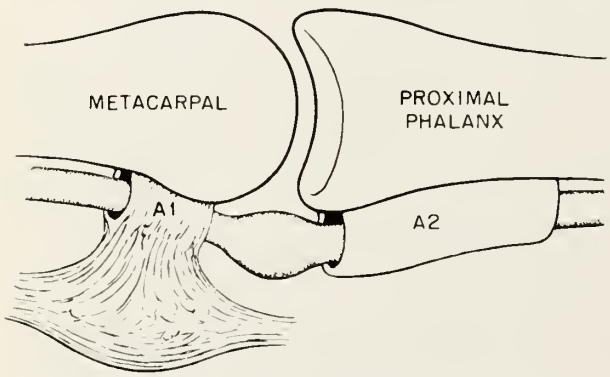


Fig. 2. Drawing emphasizes vertical extension of thickened palmar fascia involving the A-1 pulley causing stenosis of its canal.

the contracted palmar fascia by way of the vertical fibers to the A-1 pulley resulted in narrowing of the canal through the pulley and subsequent stenosing tenosynovitis. Subtotal fasciectomy and removal of the volar part of the A-1 pulley relieved locking in all patients. The fascial contracture was relieved in all but one patient, and, despite removal of the volar portion of the A-1 pulley, no subsequent bowstringing problems were encountered.

Symptoms of pain and locking and the presence of a nodule near the distal palmar crease led referring physicians to the diagnosis of trigger finger and to overlook the presence of Dupuytren's contracture despite the presence of small nodules over other metacarpophalangeal joints in three of the five patients.

In a report of Dupuytren's contracture, this group of patients is unusual in that three of the five patients were women. Dupuytren's contracture is usually a condition of men[2-5] while trigger finger is commoner in women.[3]

Table 1

Summary of Cases

Case, Age, and Sex	*Digit Involved*	*Duration of Locking*
1 76 F	Ring	6 months
2 67 F	Ring	5 years
3 60 M	Ring	1 year
4 69 F	Ring	1 year
5 58 M	Little Middle	6 months 6 months

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Perianal Paget's Disease With and Without Infiltrating Carcinoma

Report of Two Cases

WINTHROP S. MACLAUGHLIN, JR., M.D. AND ROBERTO R. MANSON, M.D.

ABSTRACT

Two additional cases of purely perianal Paget's disease are reported. The clinical presentation and divergent management of this rare entity are discussed.

In 1874, Sir James Paget reported the first case of breast cancer that was to subsequently bear his name.[1] Since that time it has become apparent that this epidermoid carcinoma may arise in apocrine tissue throughout the body, i.e., the mouth, the axilla, and the anogenital region.[2]

In 1893, Darier reported the first case of extramammary, perianal Paget's disease.[3] This clinical entity remained rare and in 1960, Grodsky reported that there were only 10 authenticated cases in the English literature.[3] Thirteen years later, Arminski and Pollard were able to collect 31 cases and added another of their own.[4] Williams, et al,[5] Sharkey, et al,[6] Jackson,[7] and Grow, et al[1] were able to contribute additional cases and at the present time, it appears that there are 43 cases of purely perianal Paget's disease reported in the English literature. It is the purpose of this paper to describe two additional patients with perianal Paget's disease who represent the spectrum of this condition.

CASE REPORTS

Patient 1

This patient is a 69-year-old white male who presented to this clinic on 11/25/77, with a six-month history of pruritus ani. There was past history of hypertension and polymyositis treated with steroids. Pertinent physical examination at this time showed erythematous raised plaques located circumferentially about the anus (Fig. 1) Proctoscopy to 15 cm. was negative. A biopsy of one of the plaques showed hyperkeratosis, parakeratosis, achanthosis and papillomatosis. In the basal portions of the epidermis were a moderate number of polyhedral cells with pale cytoplasm and round, slightly irregular nuclei with irregular chromatin pattern (Fig. 2). Staining of the epithelium with PAS revealed that the clear cells contained an abundant amount of PAS positive material which was diastase resistant.

The diagnosis was extramammary Paget's disease with circumanal involvement. A colon x-ray showed marked diverticulosis but was otherwise negative. A mechanical bowel preparation was done and the patient was given Keflin® prophylactically. The patient was taken to the operating room where examination showed that the Paget's disease extended up to the dentate line. At that time, it was decided to proceed with a radical excision of the involved perianal skin. The mucosa just proximal to the dentate line was sutured in position with 00 chromic catgut. A circumferential incision was made about the anus to include the full extent of the Paget's disease. These two incisions were then connected and the specimen was then carefully dissected and removed in a funnel-shaped fashion. The rectal sphincters were spared. A split thickness skin graft from the right thigh was then applied and secured in position with 000 Dexon® and skin clips (Fig. 3).



Fig. 1. (Patient 1) Perianal Paget's disease appearing as white elevated, erythematous plaques.

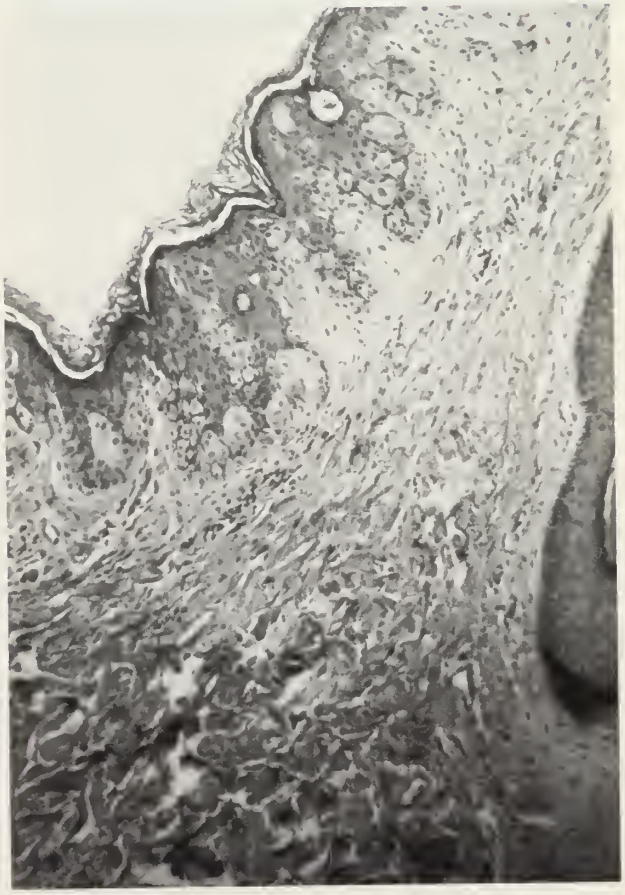


Fig. 2. (Patient 2) Low power photomicrograph showing Paget's cells in the epidermis without an underlying carcinoma.



Fig. 3. (Patient 1) Immediate postoperative appearance of split-thickness skin graft.



Fig. 4. (Patient 2) Perianal Paget's disease described by the patient as being a lump.

Pathologic examination of the specimen showed extramammary Paget's disease with margins free. The dysplastic process was limited to the epidermis and numerous sections performed, failed to reveal invasive carcinoma. Post-operatively the patient was given Codeine Sulfate and maintained on total paretcral nutrition with Aminosyn® in order to avoid disruption of the graft. The majority of the graft healed well. The patient had partial incontinence for flatus and liquid stool secondary to disruption of the normal sensory reflex, but this has improved since his dismissal. There has been no sign of tumor recurrence six months from the time of the operation.

Patient 2

This patient is a 79-year-old white male who was admitted to Hospital "A" on February 16, 1978. In 1970, the patient had excision of a malignant rectal polyp at another hospital followed by a transrectal resection of the surrounding mucosa and fulguration of the base. The exact location of the malignancy could not be determined from the previous operative record. In 1973, a local excision of a recurrent tumor at the mucocutaneous junction was performed. The pathological examination of this specimen showed it to be a 1.8 cm. neoplasm with a .5 cm. stalk. The diagnosis was adenocarcinoma of the rectum with invasion of the stalk. In 1977, he developed a "perianal lump" (Fig. 4) that was biopsied by his local physician which showed adenocarcinoma. With this diagnosis, the patient was referred to Hospital "A" for evaluation. Pertinent physical examination on admission showed circumferentially located erythematous white plaques with induration in the anal canal (Fig. 4). Initial lab work showed that the CBC, and screening tests of the liver, kidney and serum electrolytes were normal. A chest x-ray was negative. A colon x-ray showed marked diverticulosis. Microscopic examination of the biopsy of the "perianal lump" showed infiltrating nests and masses of neoplastic cells forming irregular glands (Fig. 5). The nuclei varied in size, shape and staining. The squamous epithelium showed large vacuolated cells consistent with Paget's cells infiltrating the entire thickness with infiltrating adenocarcinoma, grade II to III.

The patient was taken to the operating room on February 20, 1978, and had an abdominal perineal resection. Pathologic examination of the specimen showed that in the region of the previous scar that there were multiple nests of adenoid cystic carcinoma present in the dermis. The tumor is demonstrated by mucin-filled columnar lined cells. Individual cells are noted to vary from well to moderately well differentiated. In the region of these nests, the tumor seemed to infiltrate the squamous epithelium as a Paget-type infiltrate. The final diagnosis was adenoid cystic carcinoma with associated Paget's disease of the skin.

Discussion

Purely perianal Paget's disease is an extremely rare condition and only 43 cases have been previously reported in the English literature. It usually presents as an erythematous eczema in patients complaining of pruritus. The disease usually manifests itself in the sixth decade of life and the ages of the patients previously reported have ranged from 40 to 80 years. The diagnosis is dependent upon the demonstration of signet-shaped Paget cells containing sialomucin which stains with PAS and aldehyde-fuchsin. The differential diagnosis should include Bowen's disease, malignant melanoma, basal cell carcinoma and cloacogenic-transitional cell carcinoma.

The histogenesis of this disease has been controversial. In 1960, Grodsky stated that the extramam-

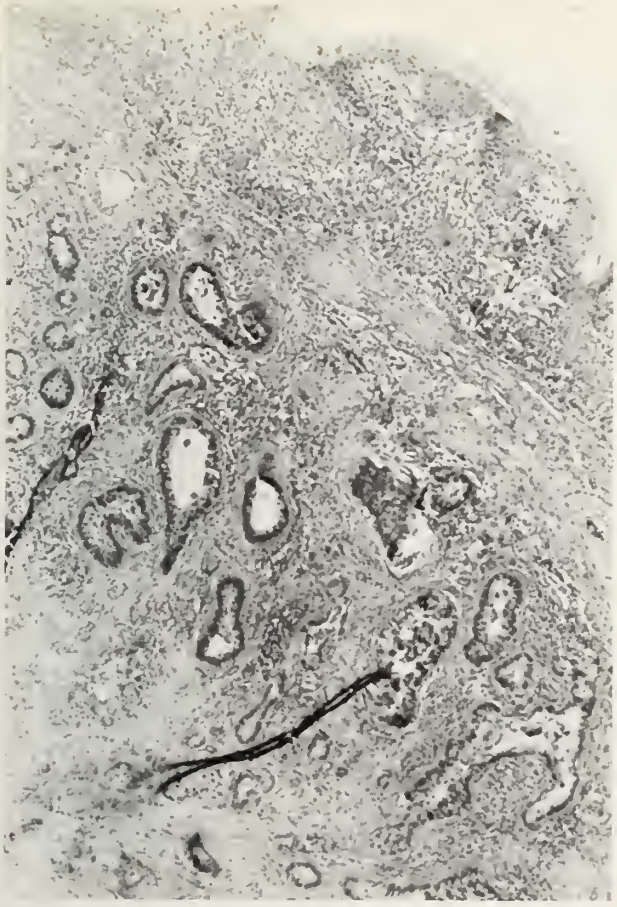


Fig. 5. (Patient 2) Low power photomicrograph showing infiltrating nests of neoplastic cells in the dermis with Paget's cells in the epidermis.

mary, perianal Paget's disease was a mucinous adenocarcinoma arising from an apocrine sweat gland or duct with cells in the epidermis as a consequence of metastases.[3] Since then, several clinical pathologic studies have provided further evidence of the apocrine origin of the disease.[8,9,10] However, the underlying carcinoma is not always demonstrable.[4] Also, it remains uncertain as to whether or not two forms of extramammary Paget's disease exist, i.e., an in situ and invasive form. Parmley believes that intraepithelial vulvar Paget's disease is a definite clinical entity and that the disease may persist for an indefinite period of time before demonstrating invasion.[11] If invasive or infiltrating carcinoma is found in association with perianal Paget's disease, the prognosis is grim as the majority of patients with invasive disease have metastases at the time of presentation. Unfortunately, most patients are diagnosed at that stage of the disease.[1]

We believe that a logical approach to treating patients suspected of having perianal Paget's disease would first include a biopsy to see whether or not the lesion was associated with an underlying carcinoma. If no underlying carcinoma were found, then wide local excision with or without skin grafting should be done. If an underlying carcinoma is found in the biopsy or in the resected specimen, then an abdominal perineal resection should be done. Groin dissection should also be considered if the nodes are clinically positive. Radiotherapy and chemotherapy appear to be of limited value in this disease.[5]

Summary

Two patients presenting with perianal Paget's disease representing the spectrum of the disease have been presented. The diagnosis and management of the disease has been discussed.

Acknowledgement

Special thanks to Drs. William Jackson and Douglas Anderson of the Department of Pathology for preparation and interpretation of the photomicrographs.

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Special Article

Another Venture in Education

Melvin Bacon, M.D.

For the past twenty-five years I have been involved in medical education in York County and Maine. This includes programs for Nurses, Physicians, as well as for the laity. Many new ideas and interesting programs have been instituted, and it is believed that we have led the way in this respect. Again, for many years I have been in a position to note many drastic changes in this field.

One thing that has irked me in recent years is the accelerating cost of postgraduate medical education nationwide. When one considers the cost of tuition, travel expense and time lost from one's practice, etc., it can be overwhelming. There are many courses I would have liked to attend, but actually they were "too rich for my blood." I just couldn't afford to attend, and I am not "crying poverty." This is one reason I have been an advocate for education close to home.

With this in mind, I would like to describe our Educational Program for the Medical Staff of the H.D. Goodall Hospital. Certain features which I believe are unprecedented will be utilized in these programs. This year I have set up six educational meetings occurring once monthly from January to June. Our meetings have been outstanding in the past, and we have had no difficulty in securing excellent speakers. Again, for years I have set up these programs without salary to myself or cost to the physicians who are members of our staff. We have invited members of other hospital staffs in York County to attend these meetings. There has also actually been very little expense or cost to our hospital. Frankly, for the most part, these programs have been subsidized by generous grants from certain drug companies. As I mentioned, this year's program will have a "new look." I have applied for credit for these courses from the American Medical Association and the American Academy of Family Physicians. (They have accredited our programs in the past.)

In addition, I have asked the President of the York County Dental Society to have this course certified by the Maine Dental Association for local dentists. The Maine Pharmaceutical Association has already approved this course for the local pharmacists. I have also sent in an application to the Maine State Nurses Association for accreditation for the nurses of our hospital who can attend these meetings. Inasmuch as we are all members of the "medical family," we should all learn together.

The program for 1979 for the Medical Staff of the H.D. Goodall Hospital is now presented for your consideration.

EDUCATIONAL PROGRAM FOR THE STAFF OF THE GOODALL HOSPITAL

Melvin Bacon, M.D.*

JANUARY—		*"Differential Diagnosis and Management of Headaches"*
Tuesday-16th	Speaker:	John A. Boothby, M.D. Maine Medical Center, Portland, ME Tufts University School of Medicine
FEBRUARY—		*"What's New in Oncology of the G.I. Tract"*
Thursday-15th	Speaker:	Michael Goldstein, M.D. Beth Israel Hospital, Boston, MA Assistant Clinical Professor of Medicine Harvard Medical School
MARCH—		*"Recognition and Management of the Acute and Chronic Brain Syndrome"*
Thursday-15th	Speaker:	Nasar Khan, M.D. Newton Wellesley Hospital, Newton Lowell Falls, MA Clinical Instructions in Psychiatry Harvard Medical School
APRIL—		*"Thyroid Disease 1979"*
Thursday-19th	Speaker:	Michael Kaplin, M.D. Thyroid Unit Peter Bent Brigham Hospital, Boston, MA Harvard Medical School
MAY—		*"Important Facets in the Diagnosis and Treatment of Liver Disease"*
Tuesday-15th	Speaker:	Robert Resnick, M.D. Beth Israel Hospital, Boston, MA Harvard Medical School
JUNE—		*"What the Physician Should Know About Occupational Disease"*
Thursday-21st	Speaker:	Larry Fine, M.D. Harvard School of Public Health Boston, MA

*Director of Medical Education, H.D. Goodall Hospital, Sanford, Maine.

These meetings will be held in the Conference Room at the H.D. Goodall Hospital on either Tuesday or Thursday nights, as indicated, and will start at 7:00 P.M.

Now we turn to another program which I started last year. During the same months as I have indicated for the above program 1979, I have arranged for a series of films which are accredited to be shown once an hour from 9:00 A.M. until 12:00, and 1:00 P.M. until 4:00 P.M., with a special showing in the evening at 6:30 P.M. Subjects to be covered in this program include hyperalimentation, management of decubitus ulcers, diabetes, chest pain, acupuncture, etc. Nurses on the staff of our hospital are also invited to attend

these programs.

I recommended to the powers to be of our hospital that they provide video tape equipment, and they are going to do this. This is another excellent medium for securing credits for postgraduate education, which would cost the physician nothing and would be an easy way for one to meet with the educational requirements of the American Medical Association, Maine Medical Association, and the American Academy of Family Practice.

There are other ways in which this endeavor could be made much easier for the physician. I have had the opportunity to review the budget of several groups in Maine who raise considerable sums of money in fund raising programs as well as grants. Without being derogatory, I am amazed at how little they contribute to professional education. It is my opinion that such groups should become more involved in this type of education by subsidizing it. This is another instance in which by their presentation of programs they could lower the cost of such education to the physicians.

I recently made a couple of suggestions to Henry J. Wheelwright, M.D., who is Chairman of the Committee on Continuing Education for the Maine Medical Association. These are that the Maine Medical Association should become an accrediting group for postgraduate education in Maine, as is done in other states, and that a publication should be put out whereby all the educational opportunities in Maine could be published. I am sure that there are many other programs going on in Maine which many physicians do not know about. This is also an easy way in which to obtain postgraduate accreditation. There are several groups in Maine that come to mind who have fallen in line with my way of thinking. The courses are relatively inexpensive and in some instances are put on at no cost to the physician. They are the Maine Academy of Family Physicians and the Lewiston groups; namely, St. Mary's General Hospital and Central Maine Medical Center. They have put on many excellent programs over the years. For quite some time now, I have been receiving a list of the excellent programs carried on at the Eastern Maine Medical Center. Dr. Brown, their Director of Education, has set up another interesting program which will occur monthly and which is comparably inexpensive starting this fall.

In conclusion, may I urge each hospital in Maine, large or small, near or far, to conduct Educational Programs* of their own if they have not done so already. (It can save the members of your staff considerable time and money.)

*N.B. For further ideas, you may refer to my article on "Trends of Education in York County" which appeared in the 1976 issue of the Journal of the Maine Medical Association, Vol. 67, No. 9, pages 287 through 288.

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Antirheumatic Agents

Ronald P. Evens, Pharm.D.

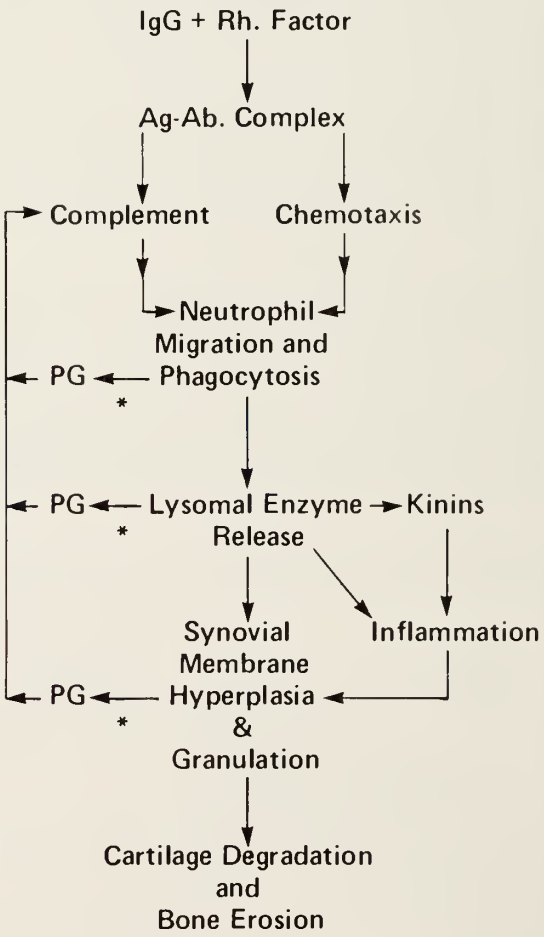
Abstract

The treatment of rheumatic disease involves the sequential use of analgesic and anti-inflammatory drugs over the long and usually progressive course of the disorder. The primary goal of therapy is control of the inflammatory process and associated symptoms. Mild analgesics such as acetaminophen, aspirin (relatively low doses), or propoxyphene may be used to control pain in early disease. Aspirin (anti-inflammatory doses), other salicylates, phenylpropionic acid derivatives (fenoprofen, ibuprofen, and naproxen), or indole derivatives (sulindac and tolmetin) are used as the disease progresses and an anti-inflammatory effect becomes essential. Aspirin remains the drug of choice, but the phenylpropionic acid or indole derivatives may be preferable in patients who cannot tolerate aspirin or other salicylates. As the disease progresses or the above drugs are no longer satisfactory, parenteral therapy with gold compounds or penicillamine may be tried. Up to six months of therapy are required before beneficial effects become evident, and these drugs have major dermatologic, renal, and hematologic toxicity in many patients. Indomethacin and phenylbutazone are usually reserved for advanced disease because of their toxicity. Alternatives to these two agents are the antimalarial drugs chloroquine and hydroxychloroquine; like the gold compounds and penicillamine, they slow the progress of the disease. Unfortunately, the antimalarial drugs may cause visual impairment. Adrenal corticosteroids and immunosuppressive drugs are reserved for the most advanced disease because of frequent and serious toxicity.

The rheumatic diseases are a group of polyarthritic disorders of unknown etiology. They include rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Reiter's syndrome. Gouty arthritis is generally considered separately since the immediate cause of the disease (hyperuricemia) is known and can be controlled with appropriate drug therapy. This paper reviews general therapeutic principles, approaches to monitoring drug effects, mechanisms of anti-inflammatory drug action, and pharmacotherapeutic considerations in the use of each antirheumatic agent.

Figure #1

Inflammation Scheme



* - sites of action of NSAIA

General Therapeutic Principles

The basic pathophysiologic process in rheumatic diseases is chronic joint inflammation,[1-5] leading to joint damage, destruction of adjacent cartilage and bone, and, eventually, joint deformities.[3,6] Prostaglandins are mediators that amplify the inflammatory process (Fig. 1). Disease activity can be assessed by the degree of inflammation, the severity and duration of pain, appearance of nocturnal pain,

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Table 1

Steps in the Drug Treatment of Rheumatic Disease

Step 1	Analgesia with aspirin (2 to 3 g/day) or acetaminophen
	Alternative drugs: phenylpropionic acid derivatives or propoxyphene
Step 2	Salicylates, phenylpropionic acid or indole derivatives
Step 3	Gold compounds or penicillamine
Step 4	Indomethacin or phenylbutazone
	Alternative drugs: antimalarials
Step 5	Adrenal corticosteroids or immunosuppressives

and the degree of morning stiffness. Rheumatic disorders are chronic and episodic, with spontaneous exacerbations and remissions, and are progressive with or without therapy. Treatment with drugs and other measures should be individualized and adjusted as the disease changes. Physiotherapeutic, surgical, orthopedic, nutritional, and psychiatric therapy may be of equal or greater importance than drug therapy, depending on the individual patient.

Goals of drug therapy include pain relief, reduction of inflammation, and preservation of functional capacity of joints and adjoining muscles; complete resolution of the pathologic process ("cure") is not a reasonable goal. Optimal disease control requires individualization of therapy based on several pharmacotherapeutic principles:[1,3,5]

1. Placebo response is of considerable importance. Over a 2-year period, oral or parenteral placebo produced a satisfactory response in more than 50% of patients in one study.[4]

2. Prior to selection of new treatments, a drug history should be taken to determine response to previous antirheumatic drug therapy.

3. Oral antirheumatic drugs should be prescribed singly at first and assessed in a serial manner in each patient until the optimal drug and dosage is found.

4. Response to antirheumatic drugs is highly variable. Some patients have the same response to different drugs, whereas others respond differently to similar drugs within the same class of compounds.

5. A single drug should be continued until sufficient time has elapsed to permit a full pharmacologic response. For example, aspirin or phenylpropionic acid derivatives should be given for one to two weeks, and penicillamine should be given for four to six months.

6. If treatment failure occurs, the drug dose, frequency of administration, and patient compliance should be considered before another drug is prescribed.

7. When treatment is successful, dosage should be reduced to maintenance levels, and, if possible, the drug should be discontinued during disease remissions.

The less toxic agents should be used in the early disease stages, with the more toxic agents subsequently added as prior drug therapy becomes less effective and the disease progresses[1,3,5] (Table 1). The first step frequently involves simple analgesic therapy. Low doses of aspirin (eg, 2 to 3 g/day) or acetaminophen may be used. Alternatively, other salicylates, phenylalkanoic acid derivatives (fenoprofen, ibuprofen, naproxen) or propoxyphene may be used.[2,7] Also, a proper balance of rest and exercise should maximize mobility and control joint trauma in the early stages.

As the disease progresses, larger doses of aspirin (3.6 to 6.0 g/day) should be used to reduce inflammation in the few involved joints—usually phalangeal and carpal joints in the hands, wrists, feet and ankles. Aspirin remains the drug of choice since no other nonsteroidal anti-inflammatory agent is more effective or less expensive.[8] However, many patients cannot tolerate large doses of aspirin for long periods. Before prescribing a non-salicylate drug, other forms of salicylate should be evaluated. Enteric-coated aspirin or sodium salicylate tablets and aspirin suppositories are erratically absorbed but may be useful. Similarly, choline salicylate (Arthropan®), choline magnesium salicylate (Trilisate®), or salsalate (Disalcid®) may be beneficial. Because they have less gastrointestinal toxicity than aspirin, phenylpropionic acid derivatives are being promoted as first choice agents.[5] However, they probably should be used only after salicylates have failed or proved too toxic. If either of these drug categories proves inadequate or too toxic, tolmetin or sulindac (indole drugs chemically related to indomethacin) can be tried.

When control of inflammation is not achieved with a nonsteroidal drug and arthritis is moderate to severe, parenteral therapy with a gold compound or penicillamine is usually indicated. These drugs are usually added to a nonsteroidal agent and can slow or arrest the pathogenic process. However, up to six months of therapy are required before full beneficial effects become evident, and these drugs have major dermatologic, renal, and hematologic effects in many patients.

Step four includes indomethacin or phenylbutazone and the antimalarials. Because of their toxicity, antimalarial drugs are usually used only after indomethacin or phenylbutazone have proven inadequate. Like gold compounds and penicillamine, antimalarials slow the progression of rheumatoid joints.

Step five includes corticosteroids or immunosuppressive agents. These drugs are reserved for patients who are unsuccessfully controlled by other drugs or who have major side effects. In patients with asymmetric, single-joint inflammation that has significantly compromised mobility, intraarticular steroids are given prior to systemic steroid therapy.

Assessment of the Disease Process and Response to Therapy

Diagnostic criteria of the American Rheumatism Association allow assessment of the degree of response to treatment.[9,10] Common subjective

parameters include joint pain, tenderness, swelling, and stiffness; these are tabulated singly or together in an articular index of active joints (e.g., "Lansbury articular index"). Each symptom is evaluated with a rating scale to quantitate improvement in the disease. Other subjective measures are the duration of morning stiffness, patient or observer preference of a particular therapy, ancillary analgesic intake, and ring size (joint size). Functional capacity is quantitated by evaluating grip strength, time required to walk 50 feet, time to onset of fatigue, time to climb a specific number of stairs, and range of joint movement with flexion and extension. Bone and joint fluid changes are assessed by x-rays, radioactive isotope uptake in joints, synovial effusions, and histologic exam of synovial specimens. Immunologic disease activity is measured by erythrocyte sedimentation rate (ESR), serum rheumatoid factors, antinuclear antibodies, and cryoglobulins.

Individual Antirheumatic Drugs

Salicylates

Aspirin. Aspirin has been the drug of choice for rheumatoid arthritis for over 30 years.[11-14]. Pain, swelling, and mobility of joints, morning stiffness, and analgesic intake are routinely improved with aspirin therapy. About one-half of patients with mild to moderate disease will be controlled by aspirin alone.[15] The standard dosage range is 3.6 to 6 grams per day. The mechanism of action of all non-steroidal anti-inflammatory agents like aspirin is inhibition of prostaglandin synthesis, which interrupts amplification of the inflammatory process (Fig. 1).

Aspirin is well-absorbed and peak plasma concentrations of salicylate are achieved within 10 to 30 minutes.[14] Although there is not a direct relationship between therapeutic response and blood levels, a salicylate concentration of 20 to 30 mg/100 ml is generally considered the therapeutic range for anti-inflammatory action.[14-16] Once an effective daily dose is found, the frequency of administration can range from every four to eight hours with acceptable small interdose blood level fluctuations. Steady-state serum levels are achieved within approximately one week after starting chronic dosing. One useful pharmacokinetic scheme[17] predicts that 650 mg given every four hours during waking hours plus a 1.3 g bedtime dose will maintain adequate blood levels throughout the 24-hour period.

In one study, buffered and enteric-coated tablets produced comparable steady-state levels, 14.0 mg/100 ml vs 17.5 mg/100 ml respectively,[18] but significant bioavailability differences have been observed between enteric-coated products.[19]

Aspirin is metabolized in the liver by both first-order and saturable processes. Saturable pathways become important during administration of the large doses required for arthritis. Small dosing increments (e.g., 325 mg) may cause disproportionately large changes in blood levels.[16] A two-fold dosage change

Continued on Page 157

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***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

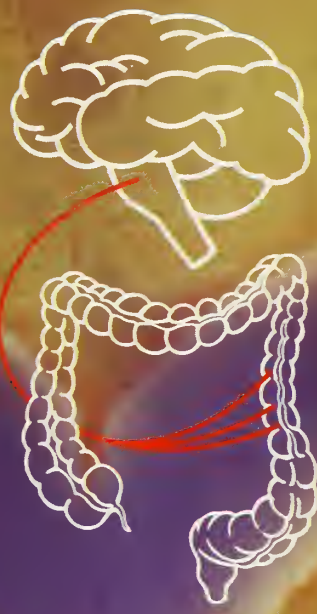
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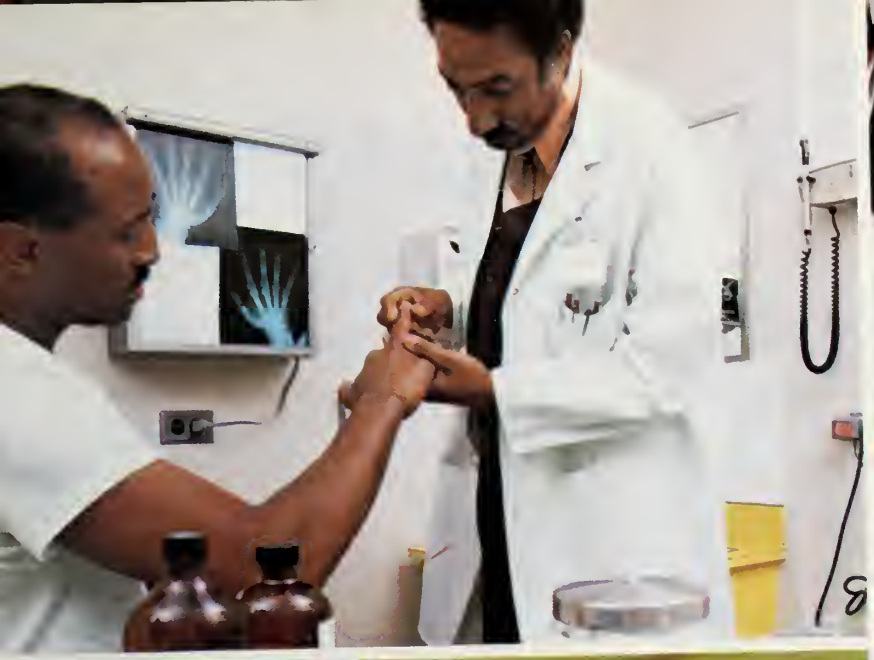
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*The safety and effectiveness of Motrin have not been established in patients with Functional Class IV rheumatoid arthritis (incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care).













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Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin* used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin (ibuprofen) is gastrointestinal (4% to 16%). This includes nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness*, headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

Incidence: Unmarked 1% to 3%, *3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Suggested dosage is 300 or 400 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day.

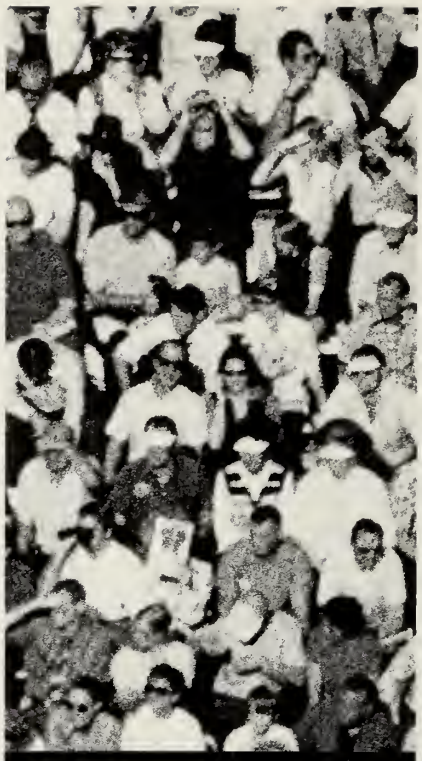
How Supplied

Motrin Tablets, 300 mg (white)	
Bottles of 60	NDC 0009-0733-01
Bottles of 500	NDC 0009-0733-02
Motrin Tablets, 400 mg (orange)	
Bottles of 60	NDC 0009-0750-01
Bottles of 500	NDC 0009-0750-02
Unit-dose package of 100	NDC 0009-0750-06
Unit of Use bottles of 120	NDC 0009-0750-26

Caution: Federal law prohibits dispensing without prescription.

NIM-3

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001



ALDOMET®
(METHYLDOPA|MSD)
TABLETS: 500 mg, 250 mg, and 125 mg
MSD
MERCK SHARP & DOHME

of 1.5 to 3.0 g per day can produce a six-fold elevation in blood levels; the plasma half-life may increase from 2-4 hours to 15-30 hours.[14]

The major problems with aspirin therapy are gastrointestinal and otologic side effects.[13,14] Gastric intolerance with dyspesia and gastritis occurs in at least 30% of arthritic patients. Occult fecal blood loss, usually 4 to 12 ml/day, is common. Tinnitus and hearing loss are usually observed only at high doses and with blood concentrations of 25 to 30 mg/100 ml or greater. Other adverse reactions include a two- to three-fold prolongation of bleeding time,[20,21] hepatotoxicity,[22] skin rashes, and asthmatic reactions.

Sodium salicylate. Sodium salicylate is as effective as indomethacin.[23] It is more rapidly absorbed than aspirin but contains substantial amounts of sodium. A 5 g daily dose provides about 31 mEq of sodium.

Choline salicylate. Choline salicylate (Arthropan) is marketed as a solution containing 870 mg of choline salicylate, equivalent to 500 mg of salicylate per 5 ml. This is about the same salicylate content as in 650 mg of aspirin. Absorption of choline salicylate is rapid because the drug is already in solution and tablet dissolution is not necessary. Thus, choline salicylate solution provides peak salicylate blood levels more rapidly than aspirin tablets.[24-27] Since the overall bioavailability of choline salicylate and aspirin are probably similar, these differences are unimportant during chronic therapy.

Published clinical trials of choline salicylate[27-31] are limited because of many methodologic inadequacies. Therefore, the efficacy and toxicity of choline salicylate versus aspirin are only empirically described and equated. Since choline salicylate is marketed as a solution, gastrointestinal side effects probably occur less often. However, bad taste limits its usefulness.

Choline magnesium salicylate. Choline magnesium salicylate (Trilisate) contains 500 mg of salicylate per tablet in the form of choline salicylate (293 mg) and magnesium salicylate (362 mg). This salicylate strength is equal to 650 mg of aspirin. The half-life of choline magnesium salicylate is dose-dependent, as with aspirin. For example, at 1 g twice daily, the half-life is 7.6 hours, whereas at 1.5 g twice daily, it is 18.3 hours.[32] Similar serum salicylate levels are produced by aspirin and choline magnesium salicylate.[33] In terms of duration of morning stiffness and joint involvement, aspirin and Trilisate are equally effective.[34]

The side effects of Trilisate are similar to those of aspirin, but they occur less often at equivalent doses.[34] The most common reactions in one study were tinnitus, 5.3%, and gastrointestinal distress, nausea, and pain, 6%.[34] Headache and hearing loss were also reported. Gastrointestinal blood loss was not evident with Trilisate, 1.5 g twice daily.[35]

The efficacy and role of choline magnesium salicylate in rheumatic diseases has not been completely established due to the very few published studies. However, preliminary evidence indicates effective twice daily dosing and fewer side effects, especially fecal blood loss.

Salsalate. Salsalate (Disalcid) is salicylsalicylic acid (500 mg/tablet). Its anti-inflammatory properties are similar to those of aspirin.[36] It is hydrolyzed to salicylic acid in vivo more slowly than aspirin[37] and has a half-life of about eight hours.[38] The rate of absorption is slower than aspirin or sodium salicylate. Steady-state salicylate blood levels of salsalate and aspirin are about equivalent (13.5 mg/100 ml at 3 g of salsalate per day versus 12.9 mg/100 ml at 3.6 g of aspirin per day).[39]

Published clinical trials of salsalate are few in number. Comparable relief of joint pain and inflammation and similar patient preference was described for salsalate and indomethacin in 18 rheumatoid arthritic patients.[40] In 20 osteoarthritis subjects, salsalate was slightly superior or equal to aspirin in six parameters of disease activity.[39] An open trial showed 73% improvement in joint pain with 66 musculoskeletal-joint disease subjects. Dosage is generally 3 g per day in three divided doses, which is a lower daily dose than aspirin (3.6 g/day) due to higher salicylate content.

Adverse effects are comparable in scope to other salicylates, e.g., dyspepsia, nausea, abdominal pain, and tinnitus. Precise frequency rates cannot be calculated due to the very few clinical trials, but they appear to be less than or equal to aspirin.[39-41] Gastric erosion and hyperemia are unusual with salsalate intake, in contrast to their common occurrence with aspirin.[42] Gastrointestinal blood loss, based on analysis of radioactive tagged red blood cells in feces,[43] and occult blood loss[44] were similarly insignificant for salsalate and placebo, but common with aspirin.

The place of salsalate in salicylate therapy for rheumatic diseases is not established. It appears to be as effective as aspirin, and it may have fewer side effects. However, its safety has not been completely described.

Phenylpropionic Acid Derivatives

Fenoprofen (Nalfon®), ibuprofen (Motrin®), and naproxen (Naprosyn®) are propionic acid derivatives marketed as antirheumatic drugs. Numerous other drugs of the same chemical class are under investigation (e.g., ketoprofen, flurbiprofen). In usual doses, fenoprofen, ibuprofen, and naproxen are well-absorbed and rapidly achieve steady-state blood levels (Table 2). All three drugs are biotransformed in the liver, and the metabolites excreted in the urine.

The relation between dose and blood levels for naproxen is linear up to approximately 500 mg/day, where the absorption process becomes saturated. Thus, higher doses produce smaller increments in blood level.[45] Food delays the absorption of all three agents and reduces peak plasma concentration (by about 30%) and total absorption (by about 20%), as does coadministration of aspirin or antacids.[45-51]

Table 2

Biopharmaceutics of Phenylpropionic Acid Derivatives

Drug	Percentage Absorption	Steady-State Plasma Concentration (μg/ml)	Half-Life (hours)	Protein Binding (%)	Metabolism (%)
Fenoprofen[5,45,46]	80	30-60 (24 hrs)	2.5-3	99	90
Ibuprofen[5,47,49]	—	—	1.9-2	95	93
Naproxen[5,50,51]	84-88	30-50 (72 hrs)	14	99	90

Table 3

Double-Blind Clinical Studies of Phenylpropionic Acid Derivatives and Aspirin in Rheumatoid Arthritis

Drug	Number of Patients		Daily Dose (g)		Duration of Studies (weeks)	Efficacy
	Drug	Aspirin	Drug	Aspirin		
Fenoprofen[53-56]	227	217	0.8-2.4	1.5-6	12-52	Fenoprofen equal to aspirin in four measures and superior in two measures. Aspirin superior to fenoprofen in three measures.
Ibuprofen[57-59]	1034	1034	0.8-1.6	3-6	4-52	Ibuprofen equal to aspirin in five measures.
Naproxen[60-62]	78	78	0.5	3.6-4	8-12	Naproxen equal to aspirin in seven measures and superior in one measure. Aspirin superior to naproxen in four measures.

Table 4

Double-Blind Clinical Studies of Phenylpropionic Acid Derivatives in Osteoarthritis

Drug	Number of Patients	Daily Dose (g)		Duration (weeks)	Efficacy
		Drug	Phenylbutazone (Ph) or Indomethacin (In)		
Fenoprofen[63]	17	2	0.3 (Ph)	4	Fenoprofen equal to phenylbutazone in pain scores.
Ibuprofen[92]	167	0.9-1.8	0.1 (In)	24	Ibuprofen similar to indomethacin in four measures.
Naproxen[64,66]	85	0.5	0.1 (In)	4	Naproxen equal to indomethacin in three measures.

Concomitant aspirin administration reduces absorption of fenoprofen by 46%[45] and naproxen by 16%.[52]

Therapeutic dosages are fenoprofen, 1.2 to 2.4 g/day in 4 divided doses; ibuprofen, 1.2 to 2.4 g/day in four divided doses; and naproxen, 500 to 1000 mg per day in 2 divided doses. All three drugs are equally effective as aspirin, indomethacin, and phenylbutazone (Tables 3 and 4). Even in direct comparisons, consistent differences among the three propionic acid derivatives are not established.[67-69] Concomitant steroid doses have been lowered by naproxen administration.[70]

Studies comparing these three agents with aspirin demonstrate a usually lower or similar frequency of adverse reactions with the phenylpropionic acid derivatives (Table 5).[55,59,62-68,71-74] The frequency of gastrointestinal ulceration and bleeding is significantly lower than with aspirin.[71-73] When naproxen was given to recent ulcer disease patients, only one out of 58 subjects had a positive stool occult blood.[75] However, all three drugs have been associated with fatal gastrointestinal hemorrhage in rare cases.[76]

Table 5

Side Effects of Phenylpropionic Acid Derivatives Versus Aspirin

	Fenoprofen vs. ASA[55]		*Naproxen vs. ASA*[62]	
Nausea	20%	40%		
Dyspepsia	23%	30%	46%	63%
Diarrhea			46%	25%
Melena			4%	8%
Tinnitus	17%	49%	21%	89%
Hearing change	1%	24%	46%	42%
Dizziness	8%	19%		
Rash	13%	9%	21%	21%
Pruritis			17%	21%
Ecchymoses			33%	63%
Headache	26%	30%	25%	38%
Drowsiness			46%	25%
Number of Patients	106		24	

months. Controlled comparisons of tolmetin with aspirin, phenylbutazone, indomethacin, and ibuprofen indicate no consistent differences in efficacy (Table 6).[83-87]

The usual effective dose in rheumatoid arthritis is 1200 mg/day in four divided doses.[69,79-84] Doses of up to 1600 mg[82-84] are effective, but one trial found no additional benefit.[80] Therapy is usually initiated at 600 to 900 mg per day and titrated upward at 200 mg increments approximately once weekly.[82,83]

Gastrointestinal reactions are the primary problem in about 25% of patients,[85] and they range from transient, mild effects like nausea to more serious reactions requiring cessation of therapy.[80] Urticaria, headache, water retention, dizziness, and hypertension have also been reported.[81,86] In comparative studies, tolmetin produced fewer side effects than aspirin[83,85] and phenylbutazone.[82] However, the side effects of tolmetin are incompletely described to date, especially the hypertensive reaction.

Table 6

Double-Blind Studies of Tolmetin Sodium in Rheumatoid Arthritis

Reference	*Number of Patients*	*Daily Dose of Tolmetin (g)*	*Daily Dose of Other Drug (g)*	*Duration (weeks)*	*Efficacy*
83	20	1.5	Aspirin 4.5	4	Tolmetin equal to aspirin in four measures. Neither drug produced change in two other measures.
84	12	1.6	Phenylbutazone 0.4	1	Tolmetin equal to phenylbutazone in three measures. Neither drug produced change in two other measures.
85	59	0.9	Aspirin 4.5	2	Tolmetin equal to aspirin in three measures. Patient preference favored tolmetin.
87	102	1.2 initially to 1.5	Ibuprofen 1.6 to 2.115	12	Tolmetin superior to ibuprofen in four measures.

Tolmetin Sodium

Tolmetin (Tolectin®) is chemically related to indomethacin and is pharmacologically similar to phenylpropionic acid derivatives.[22,69] The half-life of tolmetin is about 1 hour. Tissue distribution is minimal due to extensive (99%) binding to serum protein.[77,78] Peak plasma levels occur at 20 to 60 minutes after an oral dose.[78] Repeated drug administration (300 mg three times daily for 10 days) does not lead to significant drug accumulation.[77] Clearance is achieved primarily by hepatic biotransformation and subsequent urinary excretion of metabolites.[77] Concomitant aspirin therapy reduces tolmetin plasma levels by about 20%, but the interaction probably is not clinically important.[78]

In controlled and uncontrolled clinical trials, tolmetin is consistently superior to placebo.[79-84] Clinical response is evident after one to two weeks of therapy, but peak effects occur at two to three

Indomethacin

Indomethacin (Indocin®) is an indole compound that is well-absorbed by the oral and rectal routes. Indomethacin is approximately 90% bound to serum albumin.[88] The elimination half-life is about 6 hours. Hepatic inactivation with both renal and fecal excretion is the major means of elimination.

The clinical efficacy of indomethacin in rheumatic diseases is considerably more impressive in uncontrolled trials (62% good to excellent response) than in controlled studies (25% response).[89] Indomethacin shows no consistent superiority over aspirin, the phenylalkanoic acids, or phenylbutazone for rheumatoid and osteoarthritis (Table 7). The value of indomethacin in ankylosing spondylitis and gout is primarily supported by uncontrolled clinical trials.[89,98]

TABLE 7

DOUBLE-BLIND STUDIES OF INDOMETHACIN IN RHEUMATOID AND OSTEO-ARTHRITIS

Reference	*Disease*	*Number of Patients*	*Daily Dose of Indomethacin (mg)*	*Daily Dose of Other Drug*	*Duration*	*Efficacy*
90	Rheumatoid	21	50-200	Aspirin 1.6-6.4 g	1 month	Indomethacin equal to aspirin in four measures.
91	Rheumatoid	19	100	Aspirin 5 g	1 week	Indomethacin equal to aspirin in three measures.
92	Osteo	167	75-150	Ibuprofen 900-1800 mg	6 months	Indomethacin preferred by 54%; ibuprofen, 45%. Indomethacin provided pain relief in 63%; ibuprofen, 70%. Range of motion improved 76% among ibuprofen recipients and 68% among indomethacin recipients. Use of propoxyphene as supplemental analgesic was similar.
93	Rheumatoid	30	150	Naproxen 750 mg	4 weeks	Indomethacin equal to naproxen in six measures. Indomethacin preferred by 9 patients; naproxen by 11.
66	Rheumatoid	35	100	Naproxen 500 mg	4 weeks	Indomethacin equal to naproxen in three measures.
65	Osteo	50	100	Naproxen	8 weeks	Indomethacin equal to naproxen in four measures.
94	Rheumatoid	24	200	Phenylbutazone 300 mg	2 weeks	Indomethacin equal to phenylbutazone in two measures.
95	Rheumatoid	26	75	Phenylbutazone 300 mg	4 weeks	Indomethacin equal to phenylbutazone in four measures.
96	Rheumatoid	24	150	Phenylbutazone 300 mg	4 weeks	Indomethacin equal to phenylbutazone in eight measures.
97	Rheumatoid	18	50 mg initially, 150 mg maintenance	Phenylbutazone 300 mg	12 weeks	Indomethacin equal to phenylbutazone in five measures.

The usual daily dosage of indomethacin is 150 mg, given in two or three divided doses. This dosage level should be attained gradually, beginning with 25 mg two or three times a day and adding 25 mg in weekly increments. Daily doses higher than 150 mg are usually associated with unacceptable adverse reactions. Bedtime administration of a large part of the daily dose (e.g., 100 mg) is often useful, since it improves sleep and reduces morning stiffness and pain.[99,100] Some patients may respond after four to six days of treatment, while others require up to a month of therapy before benefit is apparent.

The frequency of adverse reactions to indomethacin is high. In one study, 50% of 228 patients reported side effects at 1.1 or 2.9 mg/kg/day.[101] Gastrointestinal symptoms and central nervous system effects are most common. Nausea (12%), diarrhea (10%), abdominal pain (3%), gastrointestinal ulcers (2%), and bleeding are the most frequent gastrointestinal effects.[89] Gastrointestinal blood loss is less than with aspirin.[102] Central nervous system effects include headache (25%), vertigo and dizziness (15%), depression, psychosis, and hallucinations.[89] Toxicity is dose-related. At daily doses of less than 150 mg, 36% of patients have adverse reactions; at 150 to 200 mg, the frequency is 60 to 70%.[89,101] About 70% of these effects occur within 48 hours of initiation of therapy.[101]

Sulindac

Sulindac (Clinoril®) is an indomethacin derivative with anti-inflammatory, analgesic, and antipyretic actions.[103] Absorption is about 90%, and peak serum levels are attained in two to three hours with single doses.[103-105] This sulfoxide compound is primarily metabolized to a sulfone, sulfone conjugates and a sulfide, which is an active metabolite.[103-106] Enterohepatic recirculation is significant with both fecal (23 to 28%) and urinary (44 to 52%) excretion, based on 96 hour collections.[103,105,106] Sulindac's half-life is seven hours, but its active sulfide has an 18 hour half-life.[103,106] This sulfide is considered to pro-

Table 8

Double-Blind Studies of Phenylbutazone in Rheumatoid and Osteo-arthritis

Reference	Disease	Number of Patients	Daily Dose of Phenylbutazone (mg)	Daily Dose of Other Drug (mg)	Duration (weeks)	Efficacy
118	Osteo	20	400	Aspirin 3,900	2	Phenylbutazone superior to aspirin in four measures and favorable in one measure.
119	Osteo	75	400	Aspirin 3,900	2	Phenylbutazone showed slight superiority over aspirin in four measures.
120	Rheumatoid	100	600	Ibuprofen 1,200	2	Phenylbutazone and ibuprofen equivalent in six measures.
121	Osteo	159	400 (Alka)	Ibuprofen 1,200	4	Phenylbutazone equal to ibuprofen in four measures.
122	Rheumatoid	24	400	Tolmetin 1,600	2	Phenylbutazone equal to tolmetin in four measures. Slightly less use of acetaminophen by tolmetin recipients. No clear differences in patient preference.

vide the majority of sulindac's action.[104]

At doses of 200 to 400 mg per day, sulindac has antirheumatic activity equal to or superior to aspirin, 3.6 to 4.8 g per day, in both rheumatoid and osteoarthritis, and to ibuprofen, 0.6 to 1.2 g per day in osteoarthritis.[104,107,108] However, these are moderate to low doses of aspirin and very low doses of ibuprofen. Sulindac is given in twice daily doses.

Side effects occur at a 25% incidence rate, but they are generally less severe than aspirin-related reactions.[104] Gastrointestinal reactions (18%) include abdominal pain, nausea, and constipation; the latter occurs more frequently than with aspirin.[104,108] Gastric mucosal erythema, edema, hemorrhage and erosion was minimal with sulindac, but common with aspirin in one study.[109] Fecal blood loss for 240 to 400 mg of sulindac was similar to placebo (0.9 ml/day) and lower than aspirin (3.6 ml/day).[110] Neurologic reactions are common and include dizziness, drowsiness, tiredness, and headache.[104,108] Dry mouth has also been reported frequently.[108] Platelet aggregation is inhibited, but this persists for only about 24 hours.[111] Bleeding time is variably reported as normal or prolonged with sulindac use.[104,111] Coadministration with tolbutamide did not alter peak serum levels or half-life of the hypoglycemic agent.[112]

Sulindac is the most recently marketed nonsteroidal, anti-inflammatory agent. Its similar antirheumatic activity and lower frequency of adverse effects in comprison to aspirin is similar to the phenylpropionic acid derivatives and tolmetin. The twice daily dosing is a convenience factor, but aspirin remains the least expensive mainstay of therapy as long as its side effects are tolerated.

Phenylbutazone

Phenylbutazone (Butazolidin®) is a pyrazolone derivative with a half-life of 37 to 76 hours.[113] Protein binding is about 98%.[4] As the dose increases, plasma levels increase, but not linearly. Plasma levels do not correlate with clinical response,[114,115] but higher doses provide greater relief than lower doses.[116] Phenylbutazone is biotransformed in the liver to several products, including an active metabolite, oxyphenbutazone.[4] The clinical effects of oxyphenbutazone (Tandearil®) are almost identical to those of phenylbutazone.[117]

Phenylbutazone is not consistently more effective than other antirheumatic agents, with the possible exception of aspirin in osteoarthritis (Tables 7 and 8).

Phenylbutazone is usually given in a daily dose of 200 to 400 mg, divided into two to four doses. As with other orally administered antirheumatic drugs, dosing with meals reduces gastrointestinal side effects.

Phenylbutazone is often compared to indomethacin with regard to side effects. The overall frequency of unwanted effects is lower with phenylbutazone, primarily because it causes few central nervous system problems.[96,97] However, phenylbutazone and oxyphenbutazone do cause significant gastrointestinal irritation (5.9%), including nausea, pain, stomatitis, and ulceration.[117,123] Edema has been reported in several studies,[121-123] and phenylbutazone should be used cautiously in patients with heart or renal disease.

The most serious adverse reaction is bone marrow depression (e.g., leukopenia, pancytopenia, agranulocytosis, aplastic anemia); it has an estimated frequency of 1 in 80,000 to 150,000 patient-months of

treatment.[116] Aplastic anemia occurs primarily in older patients (over 50 years) after three months of therapy. Agranulocytosis occurs in younger patients, usually within the first three months of therapy. Regular blood counts are advisable during prolonged therapy, but the insidiousness and spontaneity of the blood dyscrasias limit their predictive value. Patients should be advised to stop the drug and notify their physician immediately if they develop fever, sore throat, or stomatitis.

Gold Compounds

Following the very early clinical support for gold,[124] the long-standing controversy over the safety and effectiveness of gold compounds was settled by a 30-month, double-blind, placebo-controlled trial in 1960;[125,126] their efficacy has been further confirmed in more recent reports.[127-130] Gold compounds produce a favorable response in about 75% of patients, with disease remission in 20 to 25% and lesser improvement in about 55%.[131]

All gold compounds have similar antiarthritic efficacy in adult and juvenile rheumatoid arthritis, as well as similar toxicity.[123,126,131-136] Aurothioglucose (Solganal®) is more difficult to administer accurately than is gold sodium thiomalate (Myochrysine®), because the former is marketed as a suspension in oil that requires warming and agitation to resuspend.

Single 60 mg doses of gold sodium thiomalate produce peak blood levels of 700 μg/100 ml at two to eight hours.[137-139] Steady-state gold levels of 75 to 125 μg/100 ml are maintained with 50 mg intramuscularly every three to four weeks. However, a correlation between serum levels and effectiveness or toxicity is not established.[127] Gold is about 92% bound to serum albumin.[140] Tissue distribution is prominent, and includes the liver, skin, bone, bone marrow, eyes, and reticuloendothelial system.[140] Synovial concentrations are about one-half those of serum. Excretion is very slow, proceeding with a half-life of about one week; low blood levels (10-30 μg/100 ml) persist for many months.[138,139,141,142] The routes of excretion are urine (70%) and feces (30%).

An adequate trial of chrysotherapy requires four to five months because of the need to carefully assess toxicity, as well as the slow onset of effect (8 to 12 weeks).[142,143] Therapy should begin with an intramuscular injection of 10 mg of either gold compound as a test dose. If no toxicity occurs, 25 mg is given one week later. Weekly 50-mg doses are given until a total of 0.5 to 1.0 g has been administered. If there is no response by the time 1 g has been given, the drug should be discontinued. If the patient has improved and no toxic effects have developed, dosage can be reduced to 50 mg every two weeks. In patients who have prolonged remissions, the frequency of injections can be further reduced to every three or four weeks.

Adverse reactions to gold compounds are often major and can be life-threatening.[143-145] They are dose-related—at 25 mg per week 18% of recipients have an adverse reaction; this increases to 40% at 100 mg per week. Dermatitis is the most common adverse reaction with a 20-30% incidence. This usually begins as pruritus, then progresses to almost any type of skin lesion (e.g., urticaria, maculopapular, vesicular, or purpuric rash). Concomitant stomatitis and/or eosinophilia are common. The reactions are reversible within a few weeks if the drug is discontinued. Otherwise, rash may progress to fatal exfoliative dermatitis. Thus, gold therapy should be immediately discontinued when rash occurs. Gold dermatitis may be related to the vehicle; in retrospective studies of both gold compounds administered in aqueous or oily vehicles, patients who received the aqueous preparation had a higher frequency of dermatitis.[146,147]

Nephrotoxicity has been observed in up to 17% of gold recipients.[143-145] Albuminuria and proteinuria are found initially, and they may progress to nephrotic syndrome and eventually membranous glomerulonephritis and acute tubular necrosis. Blood dyscrasias can result from bone marrow suppression and involve platelets, neutrophils, and/or erythrocytes. Ocular toxicity includes corneal chrysiasis with reversible gold deposition when the total dose exceeds 1 g. More serious cataracts, corneal ulceration and retinopathy have also occurred.[148]

D-Penicillamine

D-penicillamine (Cuprimine®) has chelating activity and has been used for many years in the treatment of Wilson's disease, heavy metal poisoning, and cystinuria. More recently it has been used to treat rheumatoid arthritis, but the mechanism of its antiarthritic action is not known.[149]

Clinical improvement with penicillamine occurs in more than 50% of patients,[150-156] but the duration of therapy preceding improvement varies from 1.5 to 6 months.[152,157] Penicillamine had similar efficacy to that of gold compounds in a direct comparison.[158]

Penicillamine causes adverse reactions (over 60% incidence) more often than gold compounds, but they are less likely to require drug discontinuation.[158] Adverse effects to penicillamine include rash (26%), thrombocytopenia (17%), proteinuria, loss of taste (28%), anorexia (12%), and nausea and vomiting (22%).[150-153] Other side effects include sore lips and swollen legs. Proteinuria is common and can progress to the nephrotic syndrome.[151,154,159] Urinary protein above two to five grams per day necessitates drug discontinuation. Agranulocytosis,[152,153] myasthenia gravis,[160] and Goodpasture's syndrome[161] are rare complications of treatment. Skin reactions are divided into early and late manifestations.[150,154,155,157,162,163] The early rash is a reversible, allergic, pruritic, morbilliform eruption, occurring within three months. The late rash occurs after five months and is a papular scaly lesion, resistant to steroids.

The dosage range of penicillamine for adults with rheumatoid arthritis is between 0.75 to 2.0 g/day.[156,157] The drug should be given after meals in

divided doses, starting at low levels. A recommended regimen is 0.25 g daily for the first 14 days, followed by increases of 0.25 g daily at bimonthly intervals so that an average maintenance dose of 0.75 to 1.5 g/day is achieved in 12 to 14 weeks. Clinical effects may require 6 to 8 weeks to be seen; therefore, longer intervals between adjustments may be appropriate. If no improvement is seen after 6 months, the patient will probably not respond.

Penicillamine should be considered as an alternative to gold, and should not be used before an adequate trial of more conventional modes of treatment. Downward adjustment in other anti-inflammatory drugs, especially steroids, is often possible after the addition of penicillamine to the drug regimen.[152,153] Due to the severe toxicity of this drug, renal function and hematologic variables must be closely monitored during treatment.

Antimalarials

Chloroquine and hydroxychloroquine (Plaquenil®) are almost always used in combination with other nonsteroidal drugs when prior therapy is inadequate or parenteral treatment is not feasible.[164,165] Onset of improvement is gradual, with initial changes after at least four weeks and maximal benefit at three to six months. Therapy is usually initiated with loading doses, e.g., chloroquine 250 mg daily at bedtime or hydroxychloroquine, 200 mg one to three times a day. Maintenance doses are lower, e.g., chloroquine 250 mg two to three times a week.

Ocular toxicity is the major complication of antimalarial therapy. These drugs concentrate in the eyes at levels 100 times greater than in plasma. Diplopia and loss of accommodation are reversible reactions. Reversible corneal opacities occur with chronic administration, but they are asymptomatic. Retinal toxicity is the most serious effect, since antimalarials accumulate in pigmented occular tissues. The incidence ranges from 0.1 to 15%. High cumulative doses, e.g., 550 g over 3 to 4 years, are associated with retinal toxicity. Fundoscopic diagnosis reveals edema and pigmentary changes. Blindness may result.

Central nervous system and neurologic effects include headache, dizziness, and neuromyopathy. Gastrointestinal effects (diarrhea and nausea) and cutaneous reactions (lichenoid patches, hyperpigmentation, and exfoliative dermatitis) can also occur.

Fenemates

Mefenamic acid (Ponstel®) occupies a very secondary place in rheumatoid arthritis therapy.[1,4,5] At doses of 750 to 1000 mg/day in three divided doses, it possesses similar analgesic and anti-inflammatory action to aspirin. However, it has no advantage with respect to side effects. Common adverse reactions include dyspepsia (33%), diarrhea (10-15%), maculopapular rashes, headache, dizziness, and drowsiness. Gastrointestinal blood loss and hemolytic anemia are unusual effects.

Corticosteroids

Systemic corticosteroids should be one of the last therapeutic alternatives because of their many serious side effects.[1-5,166] They should be used only as palliative, adjunctive treatment in patients with very resistant disease, and should be given in physiologic doses (e.g., prednisone 5 to 7.5 mg/day, with a 10 to 12 mg maximum). Steroids are given in single morning doses to minimize interference with the normal diurnal adrenal secretion. Alternate day doses are generally unsuccessful in rheumatoid disease.

A summary of untoward reactions attributable to corticosteroids is as follows:[167,168] (1) Endocrine—adrenal suppression, hyperglycemia, Cushing's syndrome; (2) Musculoskeletal—osteoporosis, myopathy; (3) Cardiovascular—fluid and electrolyte imbalances; (4) Hematologic—superinfection; (5) Ocular-glaucoma, posterior subcapsular cataracts; (6) Cutaneous—bruiseability, acne, striae; (7) Neurologic—euphoria, dependence, psychosis; (8) Gastrointestinal—gastritis.

Intraarticular corticosteroids are employed for specific asymmetric joint inflammation that restricts mobility.[166] Response is apparent within 24 hours of injection, with reduction of swelling and pain. Long-acting steroid suspensions, like triamcinolone hexacetonide or prednisolone TBA, provide effects of 2 to 4 weeks duration following single injections. The dose is dependent on the joint size, e.g., knee—1 ml, ankle—0.5 ml, phalangeal—0.1 ml. Activity of the joint should be limited for about 48 hours after injection to minimize damage, due to premature mobilization. The injection procedure employs an adjunctive topical anesthetic, withdrawal of excess fluid, and a flushing of the needle in situ to prevent placement of crystals in synovial membranes. If repeated at all, at least six to eight weeks should elapse between injections. Complications of intraarticular corticosteroid injections can be acute (e.g., septic arthritis and crystal-induced synovitis) or delayed (e.g., destructive arthropathy and cutaneous atrophy).

Immunosuppressives

Cyclophosphamide (Cytoxan®) and azathioprine (Imuran®) are highly effective agents that provide partial or complete remissions in up to 75% of severely arthritic patients. However, hematologic toxicity diminishes their value.[169-172] Immunosuppressives are usually given together with corticosteroids, which permits lower steroid doses. Response follows a latent period of three to six months after initiation of therapy. Dosage of cyclophosphamide ranges from 1 to 2.5 mg/kg/day in one or two divided doses.

Major toxicity precludes routine use of these drugs in rheumatoid arthritis. Leukopenia (2000 to 4000 per cubic mm) is routinely produced by therapeutic doses. Secondary infection, especially with herpes zoster and protozoa, is another significant limitation of immunosuppressive therapy. Hemorrhagic cystitis due to a cyclophosphamide metabolite occurs fre-

quently (up to 40% incidence) and can range from microhematuria to overt bleeding. Bedtime dosing should be avoided to prevent retention of the metabolites overnight in the bladder. Adequate hydration and frequent bladder emptying are useful means to minimize this toxicity. Gastrointestinal reactions are also common (50% incidence) and include nausea, vomiting, abdominal pain, and diarrhea. Alopecia is observed in up to 30% of these patients. Ovarian suppression with amenorrhea can occur in women.

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Continued on Page 165

Tenuate® Ⓝ
(diethylpropion hydrochloride NF)

Tenuate Dospan®
(diethylpropion hydrochloride NF) controlled-release

AVAILABLE ONLY ON PRESCRIPTION
Brief Summary
INDICATION: Tenuate and Tenuate Dospan are indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use such as those described below.
CONTRAINDICATIONS: Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result).
WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. *Drug Dependence*: Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy*: Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children*: Tenuate is not recommended for use in children under 12 years of age.
PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.
ADVERSE REACTIONS: *Cardiovascular*: Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System*: Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache, rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal*: Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic*: Urticaria, rash, ecchymosis, erythema. *Endocrine*: Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System*: Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous*: A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.
DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride): One 25 mg. tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg. tablet daily, swallowed whole, in midmorning. Tenuate is not recommended for use in children under 12 years of age.
OVERDOSAGE: Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phentolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product Information as of April, 1976

MERRELL-NATIONAL LABORATORIES Inc
Cayey, Puerto Rico 00633

Direct Medical Inquiries to
MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215, U.S.A.

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References: 1. Citations available on request – Medical Research Department, MERRELL RESEARCH CENTER, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M.T., O'Dillon, R.H., and Leyland, H.M.: A Comprehensive Review of Diethylpropion Hydrochloride. International Symposium on Central Mechanisms of Anorectic Drugs, Florence, Italy, Jan. 20-21, 1977.

Merrell

8-3921 (Y587A)

Whether overweight is a complicating factor... or just uncomplicated overweight.

Tenuate® Dospan® ℂ℣
(diethylpropion hydrochloride NF)
75 mg. controlled-release tablets



A useful short-term adjunct in an indicated weight loss program.

Overweight patients in certain diagnostic categories often require strict obesity control. Diethylpropion hydrochloride has been reported useful in obese patients with hypertension, symptomatic cardiovascular disease, or diabetes. While it is not suggested that Tenuate in any way reduces these complications in the overweight, it may have a useful place as a short-term adjunct in a prescribed dietary regimen. (Tenuate should not be administered to patients with severe hypertension; see additional Warnings and Precautions on the opposite page.)

In uncomplicated obesity.

Many patients, on the other hand, present with excess fat but no disease. While this condition is often termed uncomplicated obesity, complications of both a social and a psychologic nature may be distressingly real for the patients. In these cases, a short-term regimen of Tenuate can help reinforce your dietary counsel during the important early weeks of an indicated weight loss program.

Clinical effectiveness.

The anorexic effectiveness of diethylpropion hydrochloride is well documented. No less than 16 separate double-blind, placebo-controlled studies attest to its usefulness in daily practice.[1] And the unique chemistry of Tenuate provides "...anorexic potency with minimal overt central nervous system or cardiovascular stimulation."[2] Compared with the amphetamines, diethylpropion has minimal potential for abuse.

Tenuate—it makes sense. And it's responsible medicine.

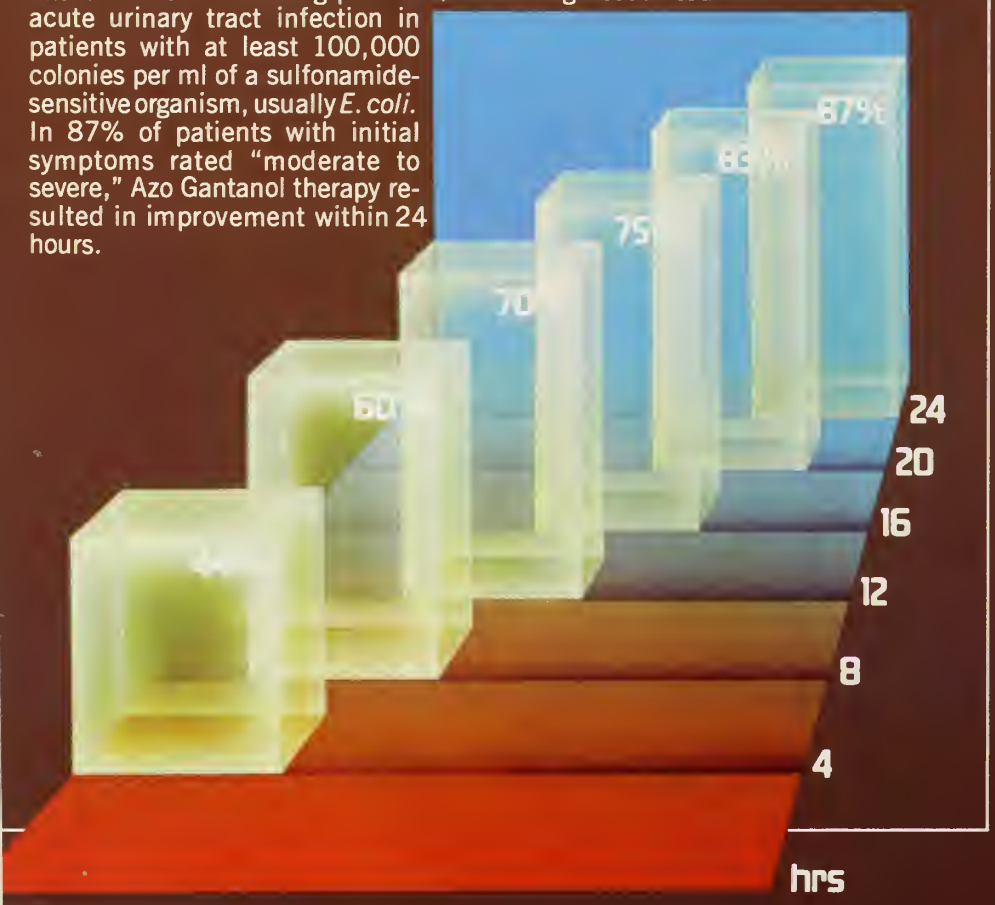
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For prescribing information see opposite page

Important data on the pain of acute cystitis:

In 87% of patients studied [303 of 349], Azo Gantanol® reduced pain and/or burning within 24 hours*

A controlled, multicenter study assessed the efficacy of Azo Gantanol in relieving pain and/or burning associated with acute urinary tract infection in patients with at least 100,000 colonies per ml of a sulfonamide-sensitive organism, usually *E. coli*. In 87% of patients with initial symptoms rated "moderate to severe," Azo Gantanol therapy resulted in improvement within 24 hours.



Before prescribing, please consult complete product information, a summary of which follows:

Indications: In adults, urinary tract infections complicated by pain (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis,* and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period; because Azo Gantanol contains phenazopyridine hydrochloride it is contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with GI disturbances.

Warnings: Safety during pregnancy not established. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, Stevens-Johnson syndrome, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *G.I. reactions* (nausea, emesis, abdominal pain, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Azo Gantanol is intended for the acute, painful phase of urinary tract infections. *Usual adult dosage:* 2 Gm (4 tabs) initially, then 1 Gm (2 tabs) B.I.D. for up to 3 days. If pain persists, causes other than infection should be sought. After relief of pain has been obtained, continued treatment with Gantanol (sulfamethoxazole) may be considered.

NOTE: Patients should be told that the orange dye (phenazopyridine HCl) will color the urine.

Supplied: Tablets, red, film-coated, each containing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 500.

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Fast pain relief plus effective antibacterial action

Azo Gantanol®

Each tablet contains 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl.

for the pain

for the pathogens

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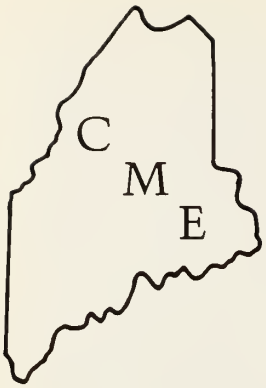
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New Blue Cross/Blue Shield/Major Medical Rates

On May 1, 1979 the Maine Medical Association's experience-rated, group health program rates will be increased to reflect the claims experience of the past two years.

Type of Contract	Total Quarterly Rate	
	Current Rate	New Rate
Individual	$122.73	$130.47
Two Person	$258.72	$313.45
Family	$287.85	$313.45
+19	$ 61.08	$ 64.98

The new rates include an increase in major medical costs occasioned by President Carter's signing into law amendments to the Civil Rights Act of 1964 which extend the prohibition against sex discrimination to disabilities which arise due to pregnancy. The effect of this regulation is 90¢ per quarter for the Individual, $3.30 per quarter for Two Person and Family and 45¢ per quarter for 19+.



CONTINUING MEDICAL EDUCATION IN MAINE

Conferences and Workshops

Title: **Legionnaire's Disease—The Vermont Experience**
Date: May 2, 1979; 10:00 A.M.
Location: Augusta Civic Center; Augusta
Sponsors: Maine Thoracic Society
Reg. Fee: None
For further information contact John Tooker, M.D.; 871-2170

Title: **Maine Medical Association's Annual Scientific Session**
Date: June 18 and 19, 1979; 9:00 A.M.
Location: Samoset Resort Inn; Rockport
Sponsor: Maine Medical Association
Credit: AMA Category I—10 hours
Reg. Fee: None
For further information contact Patricia A. Bergeron; 725-6414

Title: **Management Systems for Hospital Cost Containment**
Date: August 16-18, 1979
Location: Shawmut Inn; Kennebunkport
Sponsor: Maine Hospital Association; Maine Voluntary Cost Containment Committee
For further information contact Margery Read; 622-4794

Programs Sponsored by Mid-Maine Medical Center/Colby College

Title: **Allergy and Immunology**
Date: July 2-5, 1979
Location: Colby College
Credit: AAFP (elective)—16 hours; AMA Category I—16 hours
Reg. Fee: $250.00

Title: **Topics in Emergency Medicine**
Date: July 8-12, 1979
Location: Dean Auditorium, Mid-Maine Medical Center (MMMC)
Credit: AAFP (prescribed)—22 hours; AMA Category I—22 hours
Reg. Fee: $275.00

Title: **Epilepsy Seminar**
Date: July 10-14, 1979
Location: Colby College
Credit: AAFP (elective)—19 hours; AMA Category I—19 hours
Reg. Fee: $235.00

Title: **Topics in Pediatrics**
Date: July 15-19, 1979
Location: Colby College
Credit: AAFP (elective)—17 hours; AMA Category I—17 hours
Reg. Fee: $210.00

Title: **Surgical Techniques and Problems**
Date: July 17-20, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—15 hours
Reg. Fee: $185.00

Title: **Hematology—Disorders of Maturation and Proliferation**
Date: July 22-26, 1979
Location: Colby College
Credit: AMA Category I—18 hours
Reg. Fee: $225.00

Title: **Neurosurgical Techniques**
Date: July 22-26, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—21 hours
Reg. Fee: $260.00

Title: **Office Dermatology**
Date: July 29-August 2, 1979
Location: Colby College
Credit: AMA Category I—16 hours; AAFP (elective)—16 hours
Reg. Fee: $200.00

Title: **F.T. Hill Seminar in Otolarngology**
Date: July 29-August 2, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—18 hours
Reg. Fee: $225.00

Title: **Ophthalmology Seminar**
Date: August 5-9, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—18 hours
Reg. Fee: $225.00

Title: **Topics in Clinical Nuclear Medicine**
Date: August 12-17, 1979
Location: Colby College
Credit: AMA Category I—30 hours
Reg. Fee: $350.00

Title: **Current Aspects of Obstetrics and Gynecology**
Date: August 12-16, 1979
Location: Colby College
Credit: AMA Category I—18 hours
Reg. Fee: $225.00

Title: **Continuing Topics in Forensic Sciences**
Date: August 19-23, 1979
Location: Colby College
Credit: AMA Category I—21 hours
Reg. Fee: $275.00

Title: **Topics in Pulmonary Disease**
Date: August 19-23, 1979
Location: Colby College
Credit: AMA Category I—19 hours
Reg. Fee: $240.00
For further information on all the programs sponsored by Mid-Maine Medical Center/Colby College, contact Robert H. Kany, Ph.D.; Division of Special Programs, Colby College; Waterville, Maine 04901; 873-1131

Hospital Activities

A.R. Gould Memorial Hospital
Presque, Isle, Maine

April 30, 1979: **Common Orthopedic Problems in Infants and Young Children**
Gordon Somerville, M.D., A.R. Gould Memorial Hospital

May 7, 1979: **The Acute Abdomen**
T. O'Donnell, M.D., New England Medical Center

May 14, 1979: **Adolescent Medicine**
Steven Feldman, M.D., Brown University

May 21, 1979: **Emergency Room Dilemmas**
Siane Sixsmith, M.D., Harlem Hospital

May 28, 1979: No Meeting—Memorial Day

June 4, 1979: **Antibiotic Therapy of Intra-Abdominal Infections**
Philip B. Mead, M.D., Un. of Vt. College of Medicine

Weekly Grand Rounds are held in the Rotary Room beginning at 7:30 p.m.; programs have been certified AMA Category I. For further information contact David Skinner, M.D., 769-2511.

Augusta General Hospital
Augusta, Maine

May 22, 1979 7:30-9:30 a.m. **Infectious Disease**
Francis Tally, M.D., Tufts University School of Medicine

June 26, 1979 7:30-8:30 a.m. **Dermatology Conference**
Daniel Clarke, M.D., Augusta General Hospital

Programs have been certified AMA Category I and AAFP (prescribed). For further information contact Mrs. Nancy York; 623-4711.

Dean Hospital
Greenville, Maine

May 18, 1979 9:30 a.m.-Noon **Clinical Consultations—Gastroenterology**
Raymond Culver, M.D., Mid-Maine Medical Center (MMMC)

June 15, 1979 9:30 a.m.-Noon **Clinical Consultations—Urology**
Earle Davis, M.D., MMMC

Programs have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621.

Down East Community Hospital
Machias, Maine

May 21, 1979 7 p.m. **Advances in Rehabilitation Medicine**
Philip Mossman, M.D., Chief, Rehabilitation Services, Eastern Maine Medical Center (EMMC), and Donald Robertson, M.D., Down East Community Hospital

For further information contact Mrs. Lana Savage, R.N.; 255-3356.

Eastern Maine Medical Center
Bangor, Maine

Every Mon.	EEG Conference	12-1 p.m.
Every Mon.	Surgical Service—Chief's Rounds	5-6 p.m.
3rd Tues.	Dermatology-Pathology Conference	5-6 p.m.
3rd Tues.	Dermatology Section Meeting	6-7 p.m.
4th Tues.	Pulmonary Medicine Section Meeting	8-9 a.m.
1st Wed.	Hematology/Oncology Meeting	8-9 a.m.
Every Wed.	Tumor Clinic Conference	2-5 p.m.
Every Wed.	Radiology Conference (1) Ultrasound/Nuclear Medicine (2) Radiology Film Review (3) Neuroradiology (4) Teaching File Conference	5-6 p.m.
1st Thurs.	Ophthalmology Section Meeting	7:30-8:30 a.m.
	OB-GYN Conference (1) Pathology (2) GYN Analysis (3) OB-Pediatric Combined (4) In-Service and Education	8-9 a.m.
Every Thurs.	Pediatric Grand Rounds	9-10 a.m.
Every Thurs.	Medical Service Conference	10-11 a.m.
Every Thurs.	Cardiology Conference	11 a.m.-1 p.m.
2nd Thurs.	Orthopedic Grand Rounds	7:45-8:45 a.m.
4th Thurs.	Orthopedic Service Meeting	7:30-9 a.m.
4th Thurs.	Surgical Service Death Review	7:45-8:45 a.m.
Every Thurs.	Psychiatric Service Grand Rounds	10-11 a.m.
4th Thurs.	Urology Section Conference	7:30-8:30 a.m.
Every Fri.	Neurology Grand Rounds	8-9 a.m.

Visiting Professor Program:

2nd Thurs.	Medical Service Visiting Professor	10 a.m.-5 p.m.
2nd Thurs.	Anesthesia Service Visiting Professor	7-8 a.m.
3rd Thurs.	OB/GYN Service Visiting Professor	10 a.m.-4 p.m.
Saturdays	Surgery Service Visiting Professor	8 a.m.-Noon
4th Thurs.	Pediatric Service Visiting Professor	10 a.m.-5 p.m.
as scheduled	Orthopedic Service Visiting Professor	
as scheduled	Family Practice Visiting Professor	
as scheduled	Psychiatric Service Visiting Professor	

All activities have been certified AMA Category I. For information contact Robert H. Brown, M.D., Chairman, Med. Ed. Committee; 947-3711 Ext. 330.

Franklin County Hospital
Farmington, Maine

May 7, 1979 6-8:30 p.m. **Rehabilitation Conference**
John Diggs, M.D., Waterville and Cairbre McCaan, M.D., MMMC

May 16, 1979 12-2:30 p.m. **Visiting Professor—Psychiatry**
David Adler, M.D., Tufts University School of Medicine

All activities have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621

H.D. Goodall Hospital
Sanford, Maine

May 15, 1979 **Important Facets in the Diagnosis and Treatment of Liver Disease**
Robert Resnick, M.D., Beth Israel Hospital

June 21, 1979 **What the Physician Should Know About Occupational Disease**
Larry Fine, M.D., Harvard School of Public Health

The meetings will be held at the H.D. Goodall Hospital's Conference Room at 7 p.m. For further information contact Melvin Bacon, M.D., H.D. Goodall Hospital; 324-4310.

Mid-Maine Medical Center
Waterville, Maine

April 26, 1979 **Rheumatology Series—Rheumatoid Arthritis**
Currier McEwen, M.D., Mid-Maine Medical Center

May 3, 1979 **Electrolyte Series—Metabolic Acidosis**
Jan Drewry, M.D., Maine Medical Center

May 10, 1979 **Endocrinologic OB/GYN**
Martin Farber, M.D., Tufts University School of Medicine

May 17, 1979 **Asplenia and Sepsis**
David Ginder, M.D.; Irvin Paradis, M.D.; and Samson Fisher, M.D.

May 24, 1979 **Rheumatology Series—Gout and Pseudogout**
Currier McEwen, M.D., MMMC

May 31, 1979 **Cancer Chemotherapy**
Larry Nathanson, M.D., Tufts University School of Medicine

All programs run from 12 - 1 p.m. and have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D., 873-0621.

Plummer Memorial Hospital
Dexter, Maine

May 2, 1979 **Clinical Consultation—ENT**
1 - 4 p.m. William Diehl, M.D., MMMC

June 6, 1979 **Clinical Consultation—Pediatrics**
1 - 4 p.m. Eugene Peters, M.D.

All activities have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621.

Redington Fairview Hospital
Skowhegan, Maine

April 25, 1979 **Endocrine Treatment of Breast Cancer**
12 -1 p.m. Eugene Beaupre, M.D., MMMC, and Donald Magioncalda, Augusta General Hospital

May 30, 1979 **Visiting Professor—Pediatrics**
10:30 a.m.-2 p.m. Murray Feingold, M.D., Tufts University School of Medicine

All activities have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621.

News, Notes and Announcements

A Major and Significant Conference on Controversies in Obstetrics

The Second Robert M. True Memorial Symposium

Presented by Family Physicians and Obstetricians of the State of Maine in cooperation with the Maine Fetal Risk Project and Mead-Johnson Laboratories.

APRIL 27, 1979, at the Red Coach Convention Center, 155 Riverside St., Portland, Maine.

Guest Speaker: Norman F. Gant, Professor and Chairman, Dept. of Obstetrics and Gynecology, Univ. of Texas Medical School, Dallas, Texas.

For information on registration call 1-800-492-0645.

Statement of Robert E. McAfee, M.D., Maine Delegate to AMA, in Behalf of the M.M.A., Made Before the Board of Directors of Maine's Blue Cross and Blue Shield

We support the recommendation and commend Blue Cross/Blue Shield in its attempt to curb routine hospital admissions tests. We agree with the elimination of the 26 laboratory tests which are now considered obsolete and will continue to work with Blue Cross and Blue Shield to identify other areas of potential cost savings.

American Cancer Society National Conference—Breast Cancer—1979 September 6-8, 1979 Waldorf-Astoria Hotel New York, New York

Attendance is limited to physicians and medical students.

Advance registration is requested. There is no registration fee.

Approved for 16 credit hours in Category 1.

For further information write: Breast Cancer Conference, American Cancer Society, 777 Third Avenue, New York, New York 10017.

Tufts University School of Medicine Announces Course

Tufts University School of Medicine announces "A Review of Recent Advances in Internal Medicine" to be held May 29-June 2, 1979, at the Boston Park Plaza Hotel, Boston, Massachusetts. The program is accredited by the AMA and the AAFP.

Further information may be obtained from the Office of Continuing Education, Box 36, 136 Harrison Avenue, Boston, Massachusetts 02111.

State of Maine Department of Human Services Division of Child Health Clinic Schedule—1979

By Appointment Only

Orthopedic Clinics

Bangor—St. Joseph Hospital
9:00 a.m.: Mar. 22, Apr. 26, May 24, June 28, July 19, Aug. 23, Sept. 27, Oct. 25, Nov. 15, Dec. 20

Fort Kent—Northern Maine Medical Center
9:00 a.m.: Mar. 13, May 15, July 10, Sept. 11, Nov. 6

Houlton—Houlton Regional Hospital
10:00 a.m.: Mar. 12, May 14, July 9, Sept. 10, Nov. 5

Presque Isle—A.R. Gould Memorial Hospital
9:00 a.m.: Mar. 14, May 16, July 11, Sept. 12, Nov. 7

Waterville—Mid-Maine Medical Center (Seton Unit)
Time scheduled by hospital: Mar. 5, Apr. 2, May 7, June 4, Sept. 10, Oct. 1, Nov. 5, Dec. 3

Cleft Palate Clinic

Portland—Maine Medical Center
9:00 a.m.: May 21, June 18, Sept. 17, Oct. 15, Nov. 19

Cardiac Clinics

Bangor—St. Joseph Hospital
9:00 a.m.: Mar. 9, Apr. 13, May 11, June 8, July 13, Aug. 10, Sept. 14, Oct. 12, Nov. 9, Dec. 14

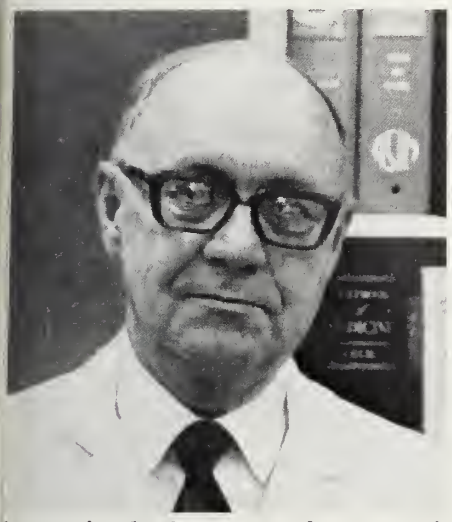
Portland—Maine Medical Center
9:00 a.m.: Mar. 2, 9, 16, 23, 30, Apr. 6, 13, 20, 27, May 4, 11, 18, 25, June 1, 8, 15, 22, 29, July 6, 13, 20, 27, Aug. 3, 10, 17, 24, 31, Sept. 7, 14, 21, 28, Oct. 5, 12, 19, 26, Nov. 2, 9, 16, 30, Dec. 7, 14, 21, 28

Children's Development Clinic

Lewiston—Central Maine Medical Center
8:30 a.m.: Mar. 12, Apr. 9, May 14, June 11, July 9, Aug. 13, Sept. 10, Nov. 26, Dec. 10

"THE PHYSICIAN IS A DECISION MAKER, AND ALMOST EVERY DECISION HE MAKES COSTS OR SAVES MONEY."

—Dr. William Felts, Past President, American Society of Internal Medicine



More and more physicians today are beginning to realize the extent of the economic influence they have, and are finding ways of holding costs down.

A number of studies show that the more physicians *know* about costs, the more they try to *reduce* them.* And this reduction can be done without reducing the quality of care to the patient.

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What else are physicians doing? Minimizing their patients' hospital stays, whenever possible. Reevaluating routine admissions procedures. Questioning the real need of the diagnostic tests they order for their patients. Avoiding duplicate testing. Trying to discourage their patients' demands for unnecessary medication, treatment or hospitalization. Compiling daily logs of their medical decisions and what they cost. And more.

More physicians today realize what a tough problem we're all faced with. They know this is a challenge for medicine. And that physicians are in the best position to deal with and solve the problem.

**PATIENT CARE Magazine—Outlook 1977, "Face-Off. Cost Containment vs. Chaos," January 1, 1977.*

Lyle CB, et al. "Practice habits in a group of eight internists," ANNALS OF INTERNAL MEDICINE 84 (May 1976), 594-601.

Schroeder SA, et al. "Use of laboratory tests and pharmaceuticals: variation among physicians and effect of cost audit on subsequent use," JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 225 (Aug. 20, 1973), 969-73.

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1979 Annual Session — June 16-19
Samoset Resort Inn
Program in This Issue

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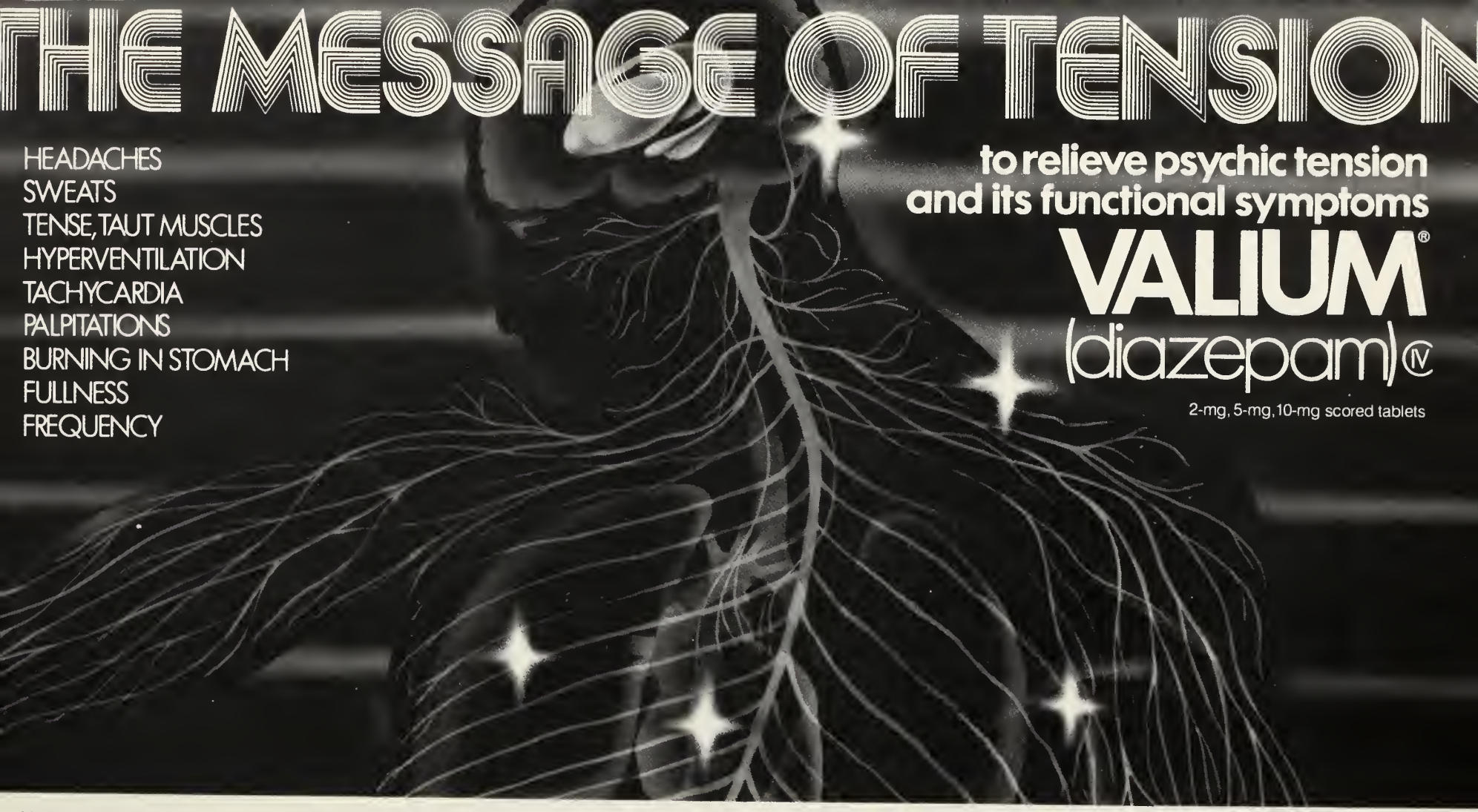
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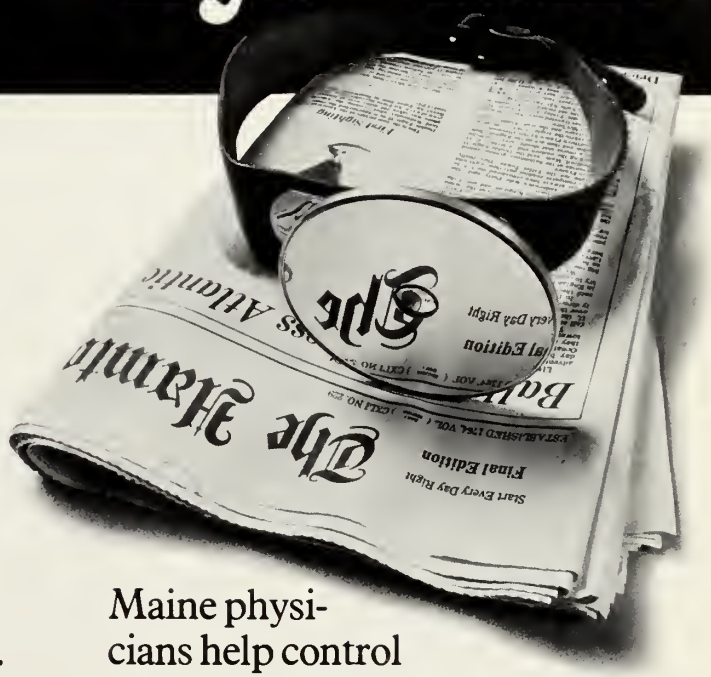
Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy.
Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals

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hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy

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Volume Seventy | Brunswick, Maine, May 1979 | Number 5

Program — 126th Annual Session
Maine Medical Association

June 16, 17, 18, 19, 1979

Samoset Resort Inn, Rockport

Arranged by the Scientific Committee

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The Scientific Program of the annual meeting of the Maine Medical Association is made possible by the cooperation and assistance of the Technical Exhibitors and the following organizations:

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Maine Society of Allergy and Clinical Immunology

Maine Society of Gastroenterology

Maine Society of Internal Medicine

Maine Neurosurgical Society

Section on Ophthalmology of the M.M.A.

Maine Society of Pathologists

Maine Chapter, American Academy of Pediatrics

Maine Psychiatric Association

Maine Urologic Association

For this cooperation and support, the members of the Scientific Committee are grateful.

Information

Registration:
Registration throughout the session will be in the Lobby at the Samoset Resort Inn.
Saturday, June 16 — 12:00 M. to 5:00 P.M.
Sunday, June 17 — 8:30 A.M. to 5:00 P.M.
Monday, June 18 — 8:30 A.M. to 5:00 P.M.
Tuesday, June 19 — 8:30 A.M. to 3:00 P.M.

Telephone: The number at the Samoset Resort Inn is Rockport, (207) 594-2511.

Meal Tickets:
For those not registering in the hotel, meal tickets must be purchased in advance by using the hotel reservation form.

Visiting Delegates:
Introduction of Visiting Delegates will take place at meetings of the House of Delegates on Saturday, June 16 and Sunday, June 17.

Technical Exhibits:
This year, thirteen companies are contributing to the success of the annual session program by participating in the Technical Exhibits. A list of the exhibiting companies and representatives will be found on page 179 of this program.
Please show your appreciation for the support of these companies by visiting these exhibits.

Badge Code:
Badges with green borders indicate Officers, Past Presidents, Delegates and Alternate Delegates of the M.M.A.; yellow borders, members of the M.M.A.; blue borders, guests; red borders, exhibitors; and plain white for the members of the Auxiliary.

Saturday, June 16

2:00 P.M. First Meeting of the House of Delegates

Call to Order: Francis I. Kittredge, M.D., President

Presiding: Speaker of the House, George W. Bostwick, M.D.

Presentation of the A. H. Robins' Physician Award for Community Service

Presentation of the Maine Blue Cross and Blue Shield "Award of Appreciation"

Speaker: H. Thomas Ballantine, Jr., M.D., Board of Trustees, American Medical Association
Subject: **Cost Containment**

6:30 P.M. Cocktails (Cash Bar)

7:30 P.M. Dinner
Dancing in the Hotel's Lounge

Sunday, June 17

7:30 to 9:00 A.M. Breakfast

8:30 A.M. Reference Committee Meetings

12:00 M. Luncheon

2:00 P.M. Second Meeting of the House of Delegates

Election of President-elect, Executive Committee District Members and AMA Delegate and Alternate Delegate

6:00 P.M. Cocktails (Cash Bar)

7:00 P.M. **Lobster Bake**
Dancing in the Hotel's Lounge

Monday, June 18

7:30 to 9:00 A.M. Breakfast

Scientific Program

Co-sponsored by the Maine Society of Internal Medicine

9:00 A.M. to 12:00 M.

Welcome — George E. Davis, Jr., M.D.

9:00 A.M. **The Physician's Assistant and the Nurse Practitioner — Why Have Them and Who Are They?**

Alfred Sadler, M.D., Boston

9:30 A.M. **The Nurse Practitioners: Their Roles — The Nurse's Perspective**

Jane W. Coolidge, RN, FNP, MS, Nurse Practitioner (PT), Employee Health/Category IV Clinic, Maine Medical Center, Portland

10:00 A.M. **Problems in the Utilization of Mid-Level Paramedical Personnel**

Edward H. Estes, Jr., M.D., Professor and Chairman, Department of Community and Family Medicine, Duke University School of Medicine, Durham

10:30 A.M. Coffee Break

10:45 A.M. **What is Joint Practice?**

Richard T. Chamberlin, M.D., Medical Director, Bingham Associates Fund and Associate Professor of Medicine, Tufts University School of Medicine, Boston

11:15 A.M. **Panel Discussion — Paramedical Personnel in Maine — Waxing or Waning?**

Moderator — George E. Davis, Jr., M.D., Augusta

Speakers:

Alfred Sadler, M.D.

Jane W. Coolidge, RN, FNP, MS

Edward H. Estes, Jr., M.D.

Richard T. Chamberlin, M.D.

John B. Madigan, M.D., Houlton — Representing the State of Maine Board of Registration in Medicine

Ms. Marion M. Klappmeier, Augusta — Representing the State of Maine Board of Nursing

12:00 M. Luncheon

Scientific Program

Sponsored by the Maine Chapter, American College of Surgeons

2:00 to 4:15 P.M.

Welcome — William P. Bristol, M.D.

Moderator — Gerard L. Morin, M.D., Lewiston

2:00 P.M. **Is the Buchwald Operation Underutilized?**

David M. Sensenig, M.D., FACS, General Surgeon, Bangor

2:15 P.M. **Use of the Intestinal Staple Device for Low Colonic Anastomosis**

Ratnakar Andalkar, M.D., FACS, General Surgeon, Norway

2:30 P.M. **Basal Cell Carcinoma of the Vulva**

John Zerner, M.D., FACS, Obstetrician and Gynecologist, South Portland

Mary Ellen Fenn, M.D., Obstetrician and Gynecologist, South Portland

2:45 P.M. **A New Technique for Vasovasostomy**

John H. Shaw, M.D., FACS, General Surgeon, Augusta

3:00 P.M. Coffee Break

3:15 P.M. **Spinal Stenosis — A New Clinical Entity**

John W. Wickenden, M.D., FACS, Orthopedic Surgeon, Rockport

3:30 P.M. **Giant Cell Arteritis**

James W. Georgitis, M.D., General Surgeon, Portland

Jeremy R. Morton, M.D., FACS, Thoracic Surgeon, Portland

3:45 P.M. **Laser Use in Ophthalmology**

Richard H. Dennis, M.D., FACS, Ophthalmologist, Waterville

4:00 P.M. **Use of Intraoperative EEG in Performing Carotid Endarterectomy**

John W. Towne, M.D., FACS, General Surgeon, Waterville

4:15 P.M. **Annual Meeting**, Maine Chapter, American College of Surgeons

Gerard L. Morin, M.D., Lewiston, President, presiding

6:00 P.M. Reception

7:00 P.M. **Annual Banquet**

Presentation of Honorary Pins

President's Address: Francis I. Kittredge, M.D.

Dancing in the Hotel's Lounge

Tuesday, June 19

7:30 to 9:00 A.M. Breakfast

Scientific Program

9:00 A.M. to 12:00 M.

Welcome — David G. Reed, M.D.

9:00 A.M. **Middle Ear Effusion — Etiology, Pathogenesis and Management**

Stephen M. Parnes, M.D., Assistant Professor, Division of Otolaryngology, The Albany Medical College of Union University, Albany

9:45 A.M. **Panel Discussion — Tonsillectomy; Adenoidectomy, Myringotomy and Tubes for the Treatment of Serous Otitis Media**

Stephen M. Parnes, M.D.

Robert H. Dixon, M.D., Otolaryngologist, Bath

Charles E. Burden, M.D., Pediatrician, Bath

10:30 A.M. Coffee Break

10:45 A.M. **The Use of Vasodilator Therapy in Cardiac Failure**

John S. Banas, Jr., M.D., Associate Professor in Medicine, Tufts University School of Medicine and Director, Cardiovascular Laboratory, Tufts-New England Medical Center Hospital, Boston

11:30 A.M. **Asthma: Newer Perspectives on Treatment**
John L. Ohman, Jr., M.D., Clinical Instructor, Harvard Medical School, Boston

Co-sponsored by Maine Society of Allergy and Clinical Immunology

12:00 M. Luncheon

Scientific Program

2:00 to 4:00 P.M.

Welcome — Dana M. Whitten, M.D.

2:00 P.M. **Drug Interaction in Anesthesia**

Kenneth W. Green, M.D., Anesthesiologist, Waterville

2:45 P.M. **Prenatal Genetic Diagnosis**

Paul H. LaMarche, M.D., Pediatrician, Bangor

3:30 P.M. Coffee Break

3:45 P.M. **Percutaneous Transhepatic Biliary Drainage and Obliteration of Gastroesophageal Varices**

Payson S. Adams, Jr., M.D., Radiologist, Portland

Specialty Group Meetings

Sunday, June 17

5:00 P.M. **SECTION ON OPHTHALMOLOGY OF THE M.M.A.**

Jou S. Tchao, M.D., Lewiston, President, presiding

Business Meeting

Monday, June 18

9:00 A.M. **MAINE UROLOGIC ASSOCIATION**

David S. Beebe, M.D., Bangor, presiding

Speaker: Carl A. Olsson, M.D., Boston

12:00 Noon — Main Dining Room

Luncheon and Business Meeting

MAINE SOCIETY OF INTERNAL MEDICINE

Leopold A. Viger, M.D., Biddeford, President, presiding

3:00 P.M. **MAINE NEUROSURGICAL SOCIETY**

Richard M. Swengel, M.D., Lewiston, presiding

Business Meeting

4:15 P.M. **MAINE CHAPTER, AMERICAN COLLEGE OF SURGEONS**

Gerard L. Morin, M.D., Lewiston, President, presiding

Annual Meeting

Tuesday, June 19

12:00 Noon — Main Dining Room

Luncheon and Business Meeting

MAINE SOCIETY OF GASTROENTEROLOGY

George E. Davis, Jr., M.D., Augusta, presiding

12:00 Noon — Main Dining Room

Luncheon and Business Meeting

MAINE SOCIETY OF PATHOLOGISTS

Kenneth E. Smith, M.D., Togus, Secretary, presiding

12:00 Noon — Sail Loft Restaurant — Luncheon

2:00 P.M. **MAINE CHAPTER, AMERICAN ACADEMY OF PEDIATRICS**

Edmund N. Ervin, M.D., Waterville, Chairman, presiding

Business Meeting

12:00 Noon — Main Dining Room — Luncheon

3:00 P.M. **MAINE PSYCHIATRIC ASSOCIATION**

Juergen Homann, M.D., Bangor, presiding

Business Meeting

1:00 P.M. **MAINE SOCIETY OF ALLERGY AND CLINICAL IMMUNOLOGY**

Samson Fisher, M.D., Waterville, President, presiding

Business Meeting

3:00 P.M. **MAINE CHAPTER, AMERICAN COLLEGE OF EMERGENCY PHYSICIANS**

Pamela P. Bensen, M.D., Lewiston, presiding

Business Meeting

HONORARY PINS

Presentation of the Association's Honorary Pins will be made by Francis I. Kittredge, M.D., President of the M.M.A., at the Annual Banquet, Monday evening, June 18 at 7:00 P.M.

FIFTY-YEAR LAPEL PINS

Fifty-Year Lapel Pins will be presented to the following members who were graduated from Medical School in 1929:

Cumberland County
Ralph Heifetz, M.D.
Tufts University School of Medicine

Janis Urjanis, M.D.
University of Latvia Faculty of Medicine

Lincoln-Sagadahoc County
Virginia C. Hamilton, M.D.
Cornell University Medical College

York County
William T. Roussin, M.D.
Boston University School of Medicine

FIFTY-FIVE-YEAR LAPEL PINS

Fifty-Five-Year Lapel Pins will be presented to the following members who were graduated from Medical School in 1924:

Androscoggin County
Merrill S. F. Greene, M.D.
Harvard Medical School

Linwood A. Sweatt, M.D.
University of Vermont College of Medicine

Cumberland County
John M. Bischoffberger, M.D.
Hahnemann Medical College and Hospital

Kennebec County
Francis H. Sleeper, M.D.
Boston University School of Medicine

Lincoln-Sagadahoc County
John M. Bachulus, M.D.
University of Vermont College of Medicine

Somerset County
Maurice S. Philbrick, M.D.
Harvard Medical School

SIXTY-YEAR LAPEL PINS

Sixty-Year Lapel Pins will be presented to the following members who were graduated from Medical School in 1919:

Aroostook County
Storer W. Boone, M.D.
McGill University Faculty of Medicine

Knox County
Sallie H. Saunders, M.D.
Tufts University School of Medicine

Piscataquis County
Norman H. Nickerson, M.D.
Bowdoin Medical School

SIXTY-FIVE-YEAR LAPEL PIN

A Sixty-Five-Year Lapel Pin will be presented to the following member who was graduated from Medical School in 1914:

Cumberland County
C. Eugene Fogg, M.D.
Bowdoin Medical School

SEVENTY-YEAR LAPEL PIN

A Seventy-Year Lapel Pin will be presented to the following member who was graduated from Medical School in 1909:

York County
Willard H. Bunker, M.D.
Bowdoin Medical School

"Medicine Avenue"

Technical Exhibits

Ayerst Laboratories, 685 Third Ave., New York, New York 10017

Boehringer Ingelheim Ltd., 90 East Ridge, P.O. Box 368, Ridgefield, Connecticut 06877
Representative: Mr. J. Pollak

Lederle Laboratories, Pearl River, New York 10965
Representatives: Mr. Rocco Maffei, Mr. Scott Keniston, Mr. Ron Hayman, Mr. Peter DeCotis and Mr. Herb Heili

Maine Blue Cross and Blue Shield, 110 Free St., Portland, Maine 04101
Representatives: Mr. Sam Barouch, Shirley Brochu, R.N., Mr. Dale McNelly, Mr. Tim Joy and Ms. Agnes Costello

Maine National Bank, 400 Congress St., P.O. Box 919, Portland, Maine 04104
Representatives: Ms. Gail C. Foust and Ms. Barbara Weldon

McNeil Laboratories, 500 Office Center Dr., Fort Washington, Pennsylvania 19034

Merck Sharp & Dohme, West Point, Pennsylvania 19486

Merrill, Lynch, Pierce, Fenner & Smith, Inc., 802 Maine Savings Plaza, Portland, Maine 04101

Pfizer Laboratories Division, 230 Brighton Rd., Clifton, New Jersey 07012
Representatives: Mr. Jerry Dorsky, Mr. Chuck Jankoski and Mr. Joe Maioriello

Reed & Carnrick Pharmaceuticals, Kenilworth, New Jersey 07033

William H. Rorer, Inc., Fort Washington, Pennsylvania 19034
Representatives: Mr. Paul E. Tondorf, Mr. Alfred L. Vogler and Mr. William E. Beever

Sandoz Pharmaceuticals, Hanover, New Jersey 07936
Representatives: Mr. Duane Jackson and Mr. Greg Fletcher

Searle Laboratories, Box 5110, Chicago, Illinois 60680
Representatives: Mr. Daniel Arimento, Mr. Al Grimes, and Mr. Jim Allott

visit the technical exhibits - BEFORE AND AFTER EACH SESSION AND DURING INTERMISSIONS

County Delegates

DELEGATES	ALTERNATES
Androscoggin County Medical Association	
Edward Z. Walworth, M.D., Secretary	
Frederick C. Holler, M.D.	Ake Akerberg, M.D.
Candace C. Walworth, M.D.	Barry D. Chandler, M.D.
August J. Valenti, M.D.	Allan M. Ingraham, M.D.
Iain D. Sanderson, M.D.	David D. Smith, M.D.
Lawrence A. Nadeau, M.D.	Donald H. Morgan, M.D.
Michael V. Rynne, M.D.	Philip J. O'Connor, M.D.
Aroostook County Medical Society	
George J. Harrison, M.D., Secretary	
Arthur D. Pendleton, M.D.	Alroy A. Chow, M.D.
William A. O'Brien, M.D.	R. Paul Johnson, M.D.
Pedro T. Simon, M.D.	Donald G. Brushett, M.D.
Cumberland County Medical Society	
Wesley J. English, M.D., Secretary	
T. James Hallee, M.D.	Albert W. Dibbins, M.D.
Bruce D. Nelson, M.D.	Stuart G. Gilbert, M.D.
Robert P. Timothy, M.D.	Michael G. Batt, M.D.
Maurice Van Lonkhuyzen, M.D.	John Zerner, M.D.
Stanley B. Sylvester, M.D.	Thomas F. Claffey, M.D.
Philip J. Villandry, M.D.	Donald A. Leeber, M.D.
Clement A. Hiebert, M.D.	Dermot N. Killian, M.D.
Patrick A. Dowling, M.D.	Noel C. Goodman, M.D.
Andrew P. Iverson, Jr., M.D.	George Geyerhahn, M.D.
John D. Kilgallen, M.D.	Frank W. Read, M.D.
David W. Haskell, M.D.	Edgar J. Caldwell, M.D.
Keith N. Megathlin, M.D.	Peter B. Webber, M.D.
Bruce R. Cassidy, M.D.	Harold N. Burnham, M.D.
Henry T. H. Grant, M.D.	Anthony L. D'Andrea, M.D.
Franklin County Medical Society	
Daniel K. Onion, M.D., Secretary	
David S. Hurst, M.D.	Gaetano T. Fiorica, M.D.
Hancock County Medical Society	
Quinby D. Gurnee, M.D., Secretary	
Chester W. Howe, M.D.	George G. Fuller, M.D.
Kennebec County Medical Association	
O. Thomas Feagin, M.D., Secretary	
Richard E. Barron, M.D.	John P. Dow, M.D.
Valentine J. Moore, M.D.	John H. Shaw, M.D.
John W. Towne, M.D.	Raymond E. Culver, M.D.
Robert A. Stram, M.D.	Howard H. Milliken, M.D.
Gareth O. M. Jones, M.D.	Peter J. Leadley, M.D.
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Earle M. Davis, M.D.	Murrill M. Szucs, Jr., M.D.
Knox County Medical Society	
Albert J. Lantinen, M.D., Secretary	
David G. Reed, M.D.	Gordon T. Paine, Jr., M.D.
Peter R. Shrier, M.D.	Roger W. Wickenden, M.D.
Lloyd Roberts, M.D.	Edward K. Morse, M.D.
Lincoln-Sagadahoc County Medical Society	
George W. Bostwick, M.D., Secretary	
Richard Evans, III, M.D.	Frank W. Sheldon, M.D.
Gerry S. Hayes, M.D.	Douglas G. Long, M.D.
Louis Bachrach, M.D.	Edward C. Schmidt, M.D.
Oxford County Medical Society	
Harbans S. Sodhi, M.D., Secretary	
Michael A. LaCombe, M.D.	Stephen B. Dewing, M.D.
Robert B. Funch, M.D.	
Penobscot County Medical Society	
James R. Curtis, M.D., Secretary	
H. Clement Jurgeleit, M.D.	Richard L. Field, M.D.
A. Dewey Richards, M.D.	Don L. Maunz, M.D.
Jack N. Meltzer, M.D.	Harry S. Tamm, M.D.
John F. Adams, Jr., M.D.	Donald G. Metzger, M.D.
Parker F. Harris, M.D.	Patrick W. Kamm, M.D.
Thomas L. Watt, M.D.	John S. Kaiser, M.D.
R. Russell Lang, M.D.	Denis T. J. Halmagyi, M.D.
Piscataquis County Medical Society	
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Somerset County Medical Society	
Vincente L. Sy, M.D., Secretary	
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Waldo County Medical Society	
Joseph A. Smith, M.D., Secretary	
Dana M. Whitten, M.D.	David D. Crofoot, M.D.
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Karl V. Larson, M.D., Secretary	
Donald M. Robertson, M.D.	Robert G. MacBride, M.D.
York County Medical Society	
Melvin Bacon, M.D., Secretary	
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Irvin Dorfman, M.D.	Ruth E. Endicott, M.D.
Robert F. Ficker, M.D.	Robert D. Vachon, M.D.

Visiting Delegates

The Connecticut State Medical Society
W. Raymond James, M.D., Essex

New Hampshire Medical Society
John M. Sherwin, M.D., Manchester

Medical Society of the State of New York
George T. C. Way, M.D., Poughkeepsie

The Rhode Island Medical Society
Robert L. Conrad, M.D., Wakefield

Vermont State Medical Society
John E. Mazuzan, Jr., M.D., Burlington

Psychiatric Drug Treatment in Children

Adair Heath, M.D.*

The treatment of children with psychiatric drugs is, at the present, more art than science. This state of affairs is the result of a number of factors, but most particularly the lack of systematic studies on the use of psychiatric drugs in large numbers of children; the lack of research expertise in the field, and strong ethical considerations in our culture make it difficult to perform any experiments on children. Because of the child's continuing growth and development, psychological and physiological factors are more complex, resulting in the lack of reliable diagnostic categories in the field of child psychiatry.[1] Because there are no real biological tests that can be used to evaluate the effectiveness of psychiatric drug treatment in children nor any clinical rating scales that are practical for the clinician, one has to rely instead on one's clinical judgement in choosing a drug and in determining the effectiveness of a given drug treatment.[2] All in all, psychiatric drug treatment in children remains one of empirically trying a given medication for an individual child displaying certain symptoms in a given environmental setting.

This article will seek to describe the general principles of psychiatric drug prescription in children, the various behavioral syndromes, the most appropriate drugs to be used in those syndromes, the most likely side effects, what behaviors the medication can most likely alter and what behaviors can most likely not be altered.

General Principles

The prescription of psychiatric drugs to children follows the same general principles as the prescription of any medication. Medication should only be used after there has been a thorough history and physical performed, indicating a clinical picture in which drug treatment appears warranted. In addition, particularly for the psychiatric treatment of children, medication should almost never be used as the sole mode of intervention. Medication is best looked at as an adjunct to treatment.[3] However, it should be pointed out that the use of psychiatric medication as another form of treatment is not contraindicated when children are in intensive psychotherapy.

Psychiatric medications will not supply new learning, will not help a child develop more adequate behaviors de novo nor are they able to stop behaviors that are deeply motivated, maintained or reinforced by the environment. Short of making a patient comatose, medication can never stop or suppress a behavior altogether. However, medication can be used to supply hope (which may or may not be the equivalent of the so-called placebo effect). Hope may be looked upon as an opportunity for the child and his significant environment to learn new behaviors for helping the child and the environment to break the negative, vicious cycle of maladaptive behavior.

It is very important for the clinician to point out before any medication is prescribed and continuously during the treatment process to the family and to the patient the already described limitations. This can be done as part of the history taking and treatment process. During the history taking, one should ascertain what problem behaviors there are, where these behaviors take place, how long they last, in what context they occur and what behaviors are desired in their place. As this picture emerges during the history taking, one selects target behaviors to be changed as a means of measuring the effectiveness of medication and also for changing the family's and the patient's mode of interaction. For instance, in trying to use medication to help a child settle down and increase his attention span, the child and the family can begin to actually count instances of target behaviors such as watching TV for an increased period of time, which the family and the child can note, and the family can appropriately reward if it takes place. Or, for instance, attention span might be increased by a parent spending time reading with the child. Not only is this providing an opportunity to measure the effect of the medication, but it is also, hopefully, supplying an opportunity for the child and the family to develop new and more rewarding modes of interacting.

At times, there may be undesirable or dangerous behaviors that need to be suppressed. It is generally not as effective to attempt to suppress a behavior altogether as it is to attempt to channel and develop a more adequate behavior in place of and out of the old maladaptive behavior. For instance, attempting to suppress a child's rambunctious and boisterous behavior which may have been labeled as hyperactive by a parent, may be futile, undesirable or unhealthy. In addition to supplying medication if this is necessary, it might also be helpful to give the parent and the child the job of finding a more adaptive means of draining off excessive energy while at the same time building up greater social skills such as playing athletic games with other children. Or, for instance, a child's losing control and physically hitting his sibling may be labeled an undesirable behavior. A chart can be kept of how often his behavior occurs and a schedule of rewards set up for a child displaying more mature ways of resolving difficulties such as using words to express feelings or appropriately seeking adult intervention.

The single most important factor for success I have found in prescribing drugs in the psychiatric treatment of children is the rapport and working alliance

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developed with the child and his family. At times, rapport is not established because one assumes that it would somehow take an inordinate amount of time to accomplish this. However, I have been surprised that even when families appear minimally motivated or frankly hostile, it is possible when one spends a few minutes with them, listening to their complaints, sifting out whether medication can be of help and pointing out with what behaviors they can expect some changes. Not only does one need to do this with the parents but I have found that even with young children one can listen and sort out or help the child to sort out that, for instance, getting angry and losing control is frightening to them and does not produce results that they enjoy. Finding and verbalizing behaviors that the family and the child would like to see changed and behaviors which also happen to be modifiable by medication maximizes the motivation and hence the chances of producing a successful outcome.

What clinical methods are there for monitoring changes in behavior? Although it is not always possible, I prefer to put off the prescription of medication for at least a week during which time one gets a baseline count of the target behaviors that one is attempting to change. After getting a baseline, one then needs to set up a way for monitoring changes in behavior by continuing counts of target behaviors. In the beginning, the child and family may need to be seen weekly until one has determined the direction of behavioral change and can set up a stable dosage level. During these follow-up visits, one can gather information about the frequency of target behaviors at home and in the school. Direct observations of the child in the office may or may not be helpful. One should always remember that the sample of behavior that one takes in the office tends not to be representative of the child's behavior in other settings. Thus, one has to rely strongly on history from the home and school.

In general, it is best to be familiar with two or more medications in each general group of medications. In prescribing one should choose one medication and start at approximately one-half the minimal recommended dose and increase the dosage at four to five day intervals (stimulants are an exception and can be increased every other day) to the point where the desired behavioral change is produced or to the point where untoward effects occur.[4] One then begins backing off on the dosage. One should go through this procedure before switching to another medication either within the same group or in another group of medications.

In general, psychotropic medications with the exception of the stimulants are long-acting. However, children, due to the greater size of their liver with respect to total body surface area and due to larger amount of non-protein bound medications, often experience a rapid buildup of potentially toxic metabolic products, thus medications are either shorter acting in children or large doses are not tolerated well.[5] For this reason, medication in children should be given several times a day rather than once a day. In general, also, one should try to settle for the smallest drug dosage that is effective. One should attempt to use drug holidays frequently such as weekends or throughout the summer, if this is possible. Hopefully, after a new repertoire of behavior skills has been developed as a mode of interaction between the child and his environment, one can attempt to stop the medication as soon as possible.

Behavioral Syndromes: Hyperactive Child

"Hyperactivity" is perhaps the best known and most widely prescribed-for psychiatric condition in children. Because stimulants have been used in this condition since approximately 1937, there is greater experience with the side effects of these medications. However, because of the extreme uncertainty of the diagnosis of hyperactivity and because of the heterogeneity of children lumped under this label, it is still very difficult to predict what child or group of children will respond favorably to what medication.[6] Studies by the use of objective measures of activity level have failed to confirm that hyperactive children are truly overactive.[7] Most studies show that the essential criteria for the majority of children helped by stimulants are that their behavior be described as disruptive, impulsive and distractable.[8] In general, these children can be described as socially immature. By lumping all of these studies together, approximately two-thirds to three-fourths of such children are helped by stimulant medication.[9] However, disruptiveness, impulsivity and distractability can stem from anxiety, frank psychosis or from an unsocialized-aggressive behavior reaction. Although some children displaying unsocialized-aggressive reactions are helped by stimulants, those displaying high anxiety levels or psychosis are generally made worse by the stimulants. However, stimulants have been found not only to be helpful for the so-called hyperactive child but also as shown by the original investigators, Bradley, Bender and Fish, to be helpful with neurotic children displaying withdrawing types of behavioral reactions.[10,11]

What behavior can the stimulants help with and what can they not? Many people have equated the hyperactive child with the learning disabled child or the "minimally brain dysfunctional" child. Stimulants do not help with raising academic achievement[12] nor do they help lessen in any permanent way the so-called neurological lags found with "minimally brain-damaged" children. Stimulants, however, can help with impulse control and attention span. They appear to work not by paradoxically calming the child but more by increasing the child's motivation, attention span and ability to inhibit undesirable behaviors.[13]

What stimulant drug choices are there for the clinician? Amphetamines come in the dextro and levorotatory isomers which appear to be equivalent

clinically in their effectiveness. However, the dextro form is preferred by most clinicians because of lesser side effects. Ritalin® (Methylphenidate) is another stimulant medication which has been found to be equal in effectiveness to the amphetamines and thought by some to have fewer side effects. Finally, Cylert® (pemoline) which although structurally different from the amphetamines or methylphenidate, acts like a stimulant clinically. One can start with either one of the amphetamines or methylphenidate. In general, the dosage of the amphetamines is approximately one-half the dosage for methylphenidate. With methylphenidate, one can start at one-half the minimal dosage, for instance, 0.15 mgs. per kilogram and increase every other day to reach a maximum (1-4 mgs. per kilogram per day) or side effects.[14]

Latency of action for both drugs is approximately thirty minutes and there is a three to six hour duration of action. Many children respond at 0.3 mgs. per kilogram of methylphenidate or approximately 10 to 15 mgs. a day.[15] Because methylphenidate is metabolized quickly, most children require a morning dose and then a second dose by noon. However, because of the side effect of insomnia, it is desirable not to give another dose after the early afternoon. Occasionally children may need a sedating antipsychotic medication such as Mellaril® at bedtime to help them to sleep. After the clinician has given an adequate trial of both methylphenidate and/or an amphetamine, one might then think about giving a trial of pemoline. Pemoline is sometimes helpful when either methylphenidate or an amphetamine has not worked. It has the advantage of a once daily dosage and is reported to have fewer side effects. However, because it is a relatively new drug, the long-term side effects are less well known.

In general, the side effects for the amphetamines, methylphenidate and pemoline are similar. They are most commonly anorexia and insomnia. In general, there is tolerance developed to these side effects and they tend to diminish after the first week or so.

However, more disturbing has been the reported long-term suppression of weight and height by prolonged use of dextroamphetamine and suppression of weight by long-term use of methylphenidate. Presumably, these effects are due to chronic anorexia.[16,17] The long-term growth effects do not appear to take place unless one goes above the 20 mgs. a day level of methylphenidate for over a year. Therefore, one should keep growth charts on children who are on stimulants for long periods of time. Weight loss over two to three months despite drug holidays and despite decreasing the dosages may be an indication for stopping the medication. Other side effects are moodiness, irritability, stomach aches, and panic with a psychotic-like toxic reaction. Panic with a psychotic-like reaction is fortunately extremely rare.

Besides the stimulants for the behavioral syndrome of hyperkinesis, other medications have been tried. In general, they are either of unestablished clinical usefulness or have not been found to be as effective as the stimulants. Anti-depressive medications apparently in the low dosages used for hyperkinetic children appear to act somewhat like the stimulants do. However, responses are more variable and there are also more serious side effects.[18] Acetylcholine stimulants like Deanol® and megavitamins have been found to be of unestablished clinical usefulness at this time.[19] There has also been described a diet free of food additives which cross-react with salycylates. So far double-blind studies have shown that this diet is slightly more effective than placebo but less so than stimulants. There is a strong question as to nutritional deficiencies developing with this diet, particularly with regard to total caloric and vitamin C intake. In addition, it appears that most families would find it difficult to follow such a diet.[20] For awhile caffeine was described as a highly effective medication for hyperactive children. However, double-blind studies have shown it is not as effective as stimulants[21] and, at today's prices of coffee, the amount of caffeine needed to produce an equivalent pharmacologic effect as an amphetamine would either be very expensive or would produce gastric irritability. The use of neuroleptic medication in the treatment of "hyperactive" children will be discussed later.

Out-of-Control Behavior

Behavior that is characterized by impulsiveness, extreme degrees of motor activity, often accompanied by moderate anxiety and poor judgment can often be helped by small dosages of neuroleptic medications. Also included in this group are those moderately disruptive children who have not responded to stimulants. The use of small dosages of neuroleptic medication to help calm out-of-control behavior illustrates again the difference between adult and child drug treatment. With adults, neuroleptic medication is generally reserved for those conditions accompanied by psychosis, particularly psychosis with thought disorder. In children, neuroleptic medication in the low-to-moderate dosage range has been found to empirically dampen excited behavior and to help control impulsive behavior in children with poor judgement.

There are three structural classes of neuroleptic medication now used in the treatment of children: phenothiazines including trifluoperazine (Stelazine®), chlorpromazine (Thorazine®), thioridazine (Mellaril); thioxanthenes such as Taractan® and Navane® and the butyrophenones such as Haldol® . Side effects of these medications include a sedating effect which must be carefully titrated because of the effect of sedation on learning. Other side effects include the anticholinergic effects of dry mouth, adynamic ileus, and urinary retention. Children seem to be particularly sensitive to the extrapyramidal side effects of many of these medications. For this reason, the butyrophenones and the piperazine type medications such as Stelazine must be

used with care. In general, it is not suggested that any anti-parkinsonian drugs such as benztropine mesylate be used prophylactically. When they are needed, after about three months, in almost all cases, they can be discontinued. Over untoward effects include cutaneous disorders, hepatic damage, aganulocytosis and lowering of the seizure threshold.[22]

Thioridazine is a widely prescribed medication, primarily because of its sedating effects and its lack of extrapyramidal side effects. In general, thioridazine, however, should be kept well below the 400 to 500 mgs. per day range, for as one gets above that level, the danger of cardiotoxic effects, lowering of the seizure threshold and retinitis pigmentosa become greater.[23]

Long-term untoward effects are still an area of limited knowledge. Weight gain with any of these medications can be a problem. However, the problem of greatest concern is tardive dyskinesia which is the insidious onset of a dyskinesia associated with worm-like movements of the tongue and protrusion of the tongue, mouth, and neck. It is thought to be due to increased sensitivity at the post-ganglionic site or actual damage to the postganglionic site from the medication. This difficulty is often masked by the medication and only appears upon withdrawal of the medication. It has primarily been described in adults, particularly older female patients on medication at high levels for many years. However, it has been described in children but so far has been reversible.[24] However, because of its danger, neuroleptic medication should be kept at the lowest possible level and the use of frequent drug holidays is encouraged. General dosage guide lines will be described in the next section.

Psychosis in Childhood and Adolescence (Childhood Schizophrenia, Infantile Autism)

Psychosis of childhood usually includes symptoms of withdrawal, bizarre thinking and language use, bizarre, stereotyped behavior, diminished reality testing, extreme psychomotor excitement, or extreme hypomotor states or anergia. In these disorders too, the difference from adult psychopharmacological treatment is pronounced. In contrast with drug treatment in adults where neuroleptic medication appears to definitely decrease relapse rates by decreasing disordered thinking, and other primary and secondary symptoms of psychosis. In children the medication is used empirically to ameliorate specific symptoms. In general, the symptoms that can be usefully treated by medication in childhood psychotic states are: motor excitement, aggressiveness, poor reality testing and poor judgement. The medication is much less useful for withdrawal and anergic type of symptoms.

The most definitive information with regard to the drug treatment of psychotic children has come out of the New York University group of Fish, Shapiro and Campbell. Campbell points out that at present there

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Tenuate® Ⓜ
(diethylpropion hydrochloride NF)

Tenuate Dospan®
(diethylpropion hydrochloride NF) controlled-release

AVAILABLE ONLY ON PRESCRIPTION
Brief Summary
INDICATION: Tenuate and Tenuate Dospan are indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use such as those described below.
CONTRAINDICATIONS: Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result).
WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle, the patient should therefore be cautioned accordingly. *Drug Dependence*: Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy*: Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children*: Tenuate is not recommended for use in children under 12 years of age.
PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.
ADVERSE REACTIONS: *Cardiovascular*: Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System*: Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal*: Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic*: Urticaria, rash, ecchymosis, erythema. *Endocrine*: Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System*: Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous*: A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.
DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride): One 25 mg. tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg tablet daily, swallowed whole, in midmorning. Tenuate is not recommended for use in children under 12 years of age.
OVERDOSAGE: Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phentolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product Information as of April, 1976

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Direct Medical Inquiries to
MERRELL-NATIONAL LABORATORIES
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Cincinnati, Ohio 45215, U.S.A.

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References: 1. Citations available on request—Medical Research Department, MERRELL RESEARCH CENTER, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M.T., O'Dillon, R.H., and Leyland, H.M.: A Comprehensive Review of Diethylpropion Hydrochloride. International Symposium on Central Mechanisms of Anorectic Drugs, Florence, Italy, Jan. 20-21, 1977.

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Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in postsympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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is no conclusive evidence on the basis of well controlled studies that drug treatment is more effective for childhood and adolescent schizophrenics than any other type of treatment.[25] Campbell repeatedly points out that drug treatment should never be the sole mode of intervention.[26] Adolescent schizophrenics tend to respond to medication much as adults. For adolescents and adults who have in some fashion proceeded through and accomplished some of life's developmental tasks, the purpose of treatment is to restore them to their normal functioning. However, for the young psychotic child whose development is not complete, one not only has to restore function but one also has to promote a climate so that arrested or delayed development of skills such as speech, etc. can develop. Whereas sedation with an adult or adolescent schizophrenic may be desirable, this may greatly impede learning in the young child who is already apathetic and withdrawn.[27] The only enduring effects of drug treatment on behavior are those areas of new and altered learning associated with psychosocial interventions such as environmental manipulation, remedial education, individual, group, parental counseling and behavior modification. Hospitalization or residential treatment may be needed depending upon the school and home needs of the individual case.[28]

Some of the antipsychotic medications that may be helpful are: the phenothiazines consisting of chlorpromazine in dosages divided two to four times a day of 9 to 200 mgs. in children under 12 years of age; thioridazine whose dosage schedule and dose range is comparable to chlorpromazine; piperizine derivatives such as trifluoperazine which is only approved by the FDA for children over six years of age. The dose range for trifluoperazine is 0.25 mgs. up to 16 mgs. daily in one to two doses a day. Dose range for the above drugs is comparable for adolescents to adult levels. Other medications used are mainly investigational at this time for young psychotic children such as: chlorprothixene (Taractan) with FDA approval for children over six years of age only. Chlorprothixene is given in a single or divided dosage from 10 to 200 mgs. daily. Thiothixene (Navane) with FDA approval for patients over 12 years of age only has both stimulating and quieting properties with a wide therapeutic margin. It can be given in one to two dosages a day from 1 to 40 mgs. daily. The butyrophenones are powerful drugs that decrease psychomotor excitement without sedation. These drugs have a very high incidence of extrapyramidal side effects. Most well known is Haldol with FDA approval for patients over 12 years of age only. It can be given in single or divided dosages from ½ to 16 mgs. daily.[29]

All of these drugs may take four to eight weeks of administration with increasing dosages until either a therapeutic effect is observed or untoward effects are reached and before an adequate determination of their effectiveness can be made. Thus, after a systematic trial of four to eight weeks, no change is observed; another drug from the same or another class of neuroleptics should be tried. In general, the length of treatment of the medication is decided on an individual basis. With acute psychosis, a month or two may be sufficient. Drug holidays are recommended when feasible, for it is believed that the intermittent stopping of the medication will reduce the risk of side effects.[30] Positive behaviors and developmental gains can be maintained after the drug is stopped, if the environment has changed in its ability to see the child in a new way and can support actively these behavioral changes. Antipsychotic medication should be discontinued during acute febrile illnesses. The side effects of these medications have been described earlier.

Gilles de la Tourette's Syndrome

This puzzling disease of unknown etiology attracts inordinate attention, especially in its full-blown form of explosive motor tics, explosive outbursts of foul language and infrequently, the presence of imitative motor and verbal patterns. While the etiology is unknown, the treatment of choice is pharmacologic treatment with haloperidol.[31] This treatment can help the child and the family to engage in other modalities of treatment which, in turn, can help prevent the emergence of the secondary problems of personality change developed in reaction to the social rejection of a child with this clinical picture. As Greenberg and Stephans point out when the question of this illness arises, diagnosis and institution of treatment should only be carried out with appropriate consultation from a child psychiatrist or at a tertiary treatment center.[32]

I will discuss briefly this rare syndrome. As a pharmacological treatment has been found, it becomes increasingly important to diagnose this syndrome early in order to prevent the emergence of secondary symptoms. In addition, I would like to point out that drug therapy is not recommended as routine treatment for common tics. Medication may be of help with common tics when they are so severe as to be incapacitating in which case the medication can be used to decrease secondarily built-up anxiety. However, differentiating common tics from this illness early on can be quite difficult.[33]

Common tics reach a peak in children between five and ten years of age and usually resolve about the time of puberty. In contrast, Tourette's Syndrome has a waxing and waning course that usually becomes more severe at puberty. Common tics are almost always limited to muscles of the face and occasionally the neck and shoulders. In contrast, progressive involvement of the arms, hands and especially the lower extremities are strong indications of Tourette's Syndrome. Common tics usually have no apparent purpose. As Tourette's Syndrome progresses, the tics become more complex and organized into bizarre and violent movements. Concurrent development of involuntary vocalizations, especially of an obscene nature, strongly suggests Tourette's Syndrome.

Laboratory tests are of really no clinical help in making the differential diagnosis.[34]

Improvement can be obtained in 90% of patients with haloperidol. The usual treatment schedule is to start at low dosages of 2 to 6 mgs. a day, increasing to levels as high as 100 to 200 mgs. a day with older adolescents or adults until either desired clinical improvements or untoward effects occur. Many patients are helped with 4 to 6 mgs. of haloperidol a day.[35] It should be remembered that haloperidol has FDA approval for children over 12 years of age only. As always, the clinician must weigh carefully the risks versus the benefits in making a judgement about treatment.

Depression

The clinical area of depression in children including phenomenology, diagnosis and treatment is very different from the adult field. In the adult field, depression is acknowledged as a prevalent condition, influenced by both genetic makeup and environmental events. In adulthood, depression is rather easily recognized as a disease state with clearly defined signs and symptoms. In childhood, particularly before puberty, the clinical syndrome of depression is not well understood, not easily recognized and therefore its treatment is not well defined.[36]

Feelings of sadness or unhappiness are quite prevalent in children. Generally, they are related to environmental events, relieved by appropriate satisfaction of the child's needs, are usually unaccompanied by ruminative guilt, depressive thinking, feelings of helplessness, suicidal preoccupation and are usually rarely accompanied by change in sleep patterns, bowel habits, loss of weight, or constipation. In addition, what few clinical trials there are have not shown that depressed children respond predictably to antidepressive medication.[37] In general, in this country the feeling is that the treatment of childhood depression involves appropriate environmental manipulation such that a child's basic needs for love and protection are met and the use of psychotherapy as indicated. Antidepressive medication has been more widely used by European child psychiatrists. When adolescence is reached, the clinical picture of depression can either remain like that of childhood or begin to assume the more adult-like picture. In addition, in adolescence the more typical adult response to antipressive medication is usually found. Generally, when antidepressives are used, they are prescribed in combination with psychotherapy and in the dosage range of 50-75 mgs. of imipramine or amitriptyline a day.[39]

Since the finding of the efficacy of lithium in the treatment of adult manic-depressive illness, there has been increasing enthusiasm in the search for a childhood form of this disease. So far, the reported cases are mainly in the midteens age group. In these reported cases, lithium has appeared to be effective in much the same way as with adults. As yet, lithium does not have the approval of the FDA for use in children below the age of 12 years. The clinical picture in the mid-teens where lithium has been helpful is one of acute onset of a psychotic illness with motor and verbal overactivity, distinct mood shifts, possible early history of biphasic mood shifts, a possible family history of manic-depressive or depressive illness, and a lack of response to antipsychotic medication.[40] Treatment with lithium of children with manic-depressive illness is currently a research issue.

Enuresis

For the purposes of this discussion, enuresis refers to involuntary wetting which can include both day wetting and night wetting. Little is known about day wetting. The age of the child is extremely important in considering whether one defines wetting as normal behavior or abnormal. In general, it appears that this is a disorder involving males much more frequently than females, in which approximately 10% of seven year olds still wet and from the age of twelve on, 3% continue to wet.[41] However, less than 3% continue to wet after the age of twenty years. Most authorities assume that in a reasonable child care environment, most children cease involuntary day wetting by the age of five years and involuntary night wetting by the age of six years.[42]

In spite of the frequency of this disorder and the real pain that it causes the children and their parents who suffer from it, our knowledge about enuresis is still far from complete. Scientific thinking about it has assumed various postures throughout this century. Recently popular was the psychogenic view which held that wetting was caused by a psychological problem in which the child attempted to express his anger or fears through wetting. Faulty and repressive toilet-training as well as various other adversive practices were imputed to the parents of these children by various workers. Lesions of the urinary tract have been looked for in the past as well as various signs of developmental immaturity. At present an elective, empirical and flexible approach appears to be the most reasonable one. Psychotherapy for this symptom alone has not been found helpful nor has blaming the parents. However, psychotherapy can be most helpful and supportive to children who have this problem in order to help prevent the secondary problems of anxiety, feelings of low self-esteem and social withdrawal until developmental immaturities work themselves out.[43]

There appear to be at least four types of night wetters. The first, and by far the largest group, are those children without organic difficulties who have never been dry and who appear to have some developmental immaturity consisting of involuntary, premature bladder contractures even with small amounts of urine in the bladder.[44] Some workers have reported abnormal sleep EEGs in these enuretics, naming these disorders of arousal.[45,46] The second largest group are those children who have learned to control wetting at some point in their life but due to some tramatic factor which at the time of referral is often

unclear, may experience a re-occurrence of wetting. Examples of precipitating stress are the birth of a sibling, marital problems in the parents, beginning school, etc. Sometimes supportive and, at other times, more exploratory psychotherapy are indicated. If these fail, antidepressive medication is helpful in this group of children. It is said that the secondary wetters show the best response to antidepressive medication.[47] The third group is a smaller category of night wetters whose bed wetting is an additional symptom and part of or a coincidental finding in a well-defined psychiatric disorder. Often these children are impulsive and aggressive. Bed wetting is not their primary problem and they need an intensive psychotherapeutic intervention for their primary psychiatric problem.[48] A final and the smallest group of night wetters are those children with urinary infections and/or congenital abnormalities of the urinary tract.[49]

The practitioner treating the bed wetter needs to take a thorough history and do a thorough physical. Often a reliable history as to whether there was a dry period or not is difficult to obtain. A dry period of several months duration points strongly against the possibility of congenital urinary abnormalities.[50] It is important to gain a history of the frequency of bed wetting in order to measure the effectiveness of any treatment. It is also important to obtain, if possible, the time of wetting, especially if it occurred before midnight or after midnight as will be explained later. The history of the parents' attitude towards the child, his wetting and the child's attitudes towards the same should be obtained. Urinanalysis should be done. It is generally felt that any further investigation such as urine culture, IVP and especially cystoscopic examination should be reserved for those cases in which abnormalities have been found on physical or urinanalysis.[51]

In addition to the use of psychotherapeutic interventions as explained before, the basic approach involves the use of one or the other or both of the following. A wetness detector with either a light or an alarm have been found helpful in many cases. This is widely used in Great Britain with about an 80% success rate for complete dryness. However, as many as one-third of these cases relapsed and many cannot be reconditioned when the device is used again.[52] In addition, there are technological problems with the fact that the urine eventually corrodes and short-circuits the detection device leading to false awakening and poor learning. In addition to the need for the child and the parent to be highly motivated enough to wake up as often as the device goes off, problems have been reported in which the buzzer fails to awaken a child who continues to lie in wet bedclothes with current flowing between the electrodes leading, at times, to skin ulcerations.[53] In addition to this wetness detector system, parental re-education and rewards for successful responses to the child can greatly augment any intervention.

The second approach is the psychological supportive-drug treatment one. After a history and physical have ruled out possible organic causes, a trial of several weeks re-education of the parent and supportive-behavioral approaches with the child can be used. First, parent and child should be reassured that wetting is a relatively common occurrence which we do not know a great deal about, that often spontaneously stops around the ages of six or twelve years and does not necessarily mean that the child is willfully trying to defy anyone. It can be pointed out that bedwetting itself is not physically harmful. Excessive parental attention either of a negative or positive type should be discouraged as it often sets up a negative vicious cycle making matters worse. The child should be encouraged and reinforced for taking responsibility for changing the sheets and putting his clothes in the hamper. A calendar can be made with the child given responsibility of keeping track of the frequency of wetting and given an agreed upon but appropriate reward if he is dry or, if necessary, if the bed is less wet than on other nights. In addition, sometimes it is helpful since urinary capacity in these children is small that the child be encouraged to urinate into a graduated cup and should be encouraged to hold his urine longer and longer to increase his bladder capacity, measuring the increased capacities in the graduated cup.

If, after several weeks or several months of this regime, there is little to no improvement, one might next try one of the antidepressive medications. Imipramine was the first drug used for enuresis and is probably the drug of choice since most people have the greatest familiarity with it. However, if the child has a concomitant sleep disturbance, then the sedative side effects of amitriptyline might be desired. If there is a therapeutic failure with one or the other drug, it is unlikely that the other one would be any more successful.

It is important to point out to the parents the limitations of drug treatment at the beginning. The first limitation is that the medication commonly produces a dramatic decrease in the frequency of wetting but much less often, a complete cessation. The second limitation is that more often than not the use of the medication does not result in any permanent improvement.[54]

The mechanism of action of the antidepressives in the treatment of enuresis is still debated and there is evidence to back up several contradictory theories. These theories include anticholinergic effects, changes in the level of sleep, placebo effects, antidepressive effect,[55] local anesthetic effect and alpha-adrenergic effect.[56]

The efficacy of drug treatment is also debated and reports run as high as from 40 to 60 percent to as low as 10 to 20 percent who become totally dry after one month of treatment. If one looks at those bedwetters who have started wetting after tramatic circumstances, the results fare much better. However, estimates of the number of patients who remain dry after cessation of medication range only from 10 to

30 percent. If one only looks at reduction in the frequency of wetting then one can see between a 56 to 79 percent reduction in frequency.[57]

Schedules and dosages of drugs vary greatly with often contradictory recommendations from the literature. Some recommend a flat 25 mgs. of imipramine for children under twelve and 50 mgs. for older children. In general, few significant differences in response to dosage level have been reported except for the side effects that are experienced. Dosages usually range somewhere between 25 to 75 mgs. a day. Because of cardio-toxic side effects, there has been a tendency now to be more cautious about high dosages. This will be discussed later. In general, it seems prudent to start children under twelve at not more than 25 mgs. a night and older children 50 mgs. a night. If, after one week there is no response, then increase gradually for children under twelve to a maximum of probably 3 mgs. per kilogram per day and to probably not more than 100 mgs. a day for older children. There is some evidence that children who wet before midnight are helped with an early evening administration, since the anti-cholinergic effect peaks three hours after administration. If, the wetting occurs after midnight then an H.S. administration can be used. Recommendations about the duration of treatment with antidepressives vary from a minimum of one month to the idea of maintenance therapy. Many workers feel that treatment should be limited to six months.[58]

Side effects of the medication at dosages recommended are primarily the anticholinergic side effects of dry mouth and sedation; occasional nightmares, daytime change in mood to irritability. More serious side effects are the cardio-toxic side effects with changes in cardiac conduction. This has led the FDA to only approve imipramine for enuresis in investigational protocols whose total daily dose does not exceed 5 mgs. per kilogram and then only with careful EKG monitoring. However, the 3 mgs. per kilogram per day level is felt to be safer for enuresis.[59]

School Phobia or Extreme Separation Anxiety

Although it may seem surprising in view of the predominate psychodynamic theories of etiology and treatment of these symptoms, there has been increasing attention to the physiological differences of neurotic individuals experiencing this degree of anxiety and the pharmacological treatment of these conditions. As more and more experience is gained with children demonstrating school refusal particularly those with intractable forms, it is becoming apparent that there is more than one type of child exhibiting this behavior.[60] Gittelman-Klein talks about her use of imipramine in the treatment of extreme anxiety experienced by children manifesting school refusal. It should be pointed out that this is basically an investigational frontier in the field. At best medication is an adjuctive approach in addition to active environmental manipulation, behavioral approaches, individual treatment, family treatment and/or parental counseling. The doses recommended have usually equalled or exceeded the FDA's guidelines of 5 mgs. per kilogram per day level.[61]

Night Terrors

Night terrors to be differentiated from nightmares are disassociated panic states occuring when a child, usually a boy, arouses suddenly from stage four sleep. The child is usually unresponsive to reassurance and appears to be in absolute terror until the episode is over. Often there is amnesia for the event. Some workers feel that these disorders are associated with sleepwalking and enuresis. Most cases clear spontaneously with reassurance and/or environmental manipulation. Some follow-up data indicates that those that do not clear up on their own occur in people with vulnerabilities to later development of character disorders. It has been found that those children who do not respond spontaneously will respond to small dosages of diazepam or Valium (2 to 5 mgs.) Others have described response to small dosages of antipressives.[62] However, in view of the more serious side effects of antidepressives, it seems preferable to use diazepam if possible.

Mild to Moderate Anxiety States

Anxiety in children is usually situation-dependent, acute and often responds to placebos, especially reassurance and to environmental changes that increase a child's feelings of security and mastery. Thus, the use of medication should, in most instances, be discouraged for children experiencing these states. Rather one should look for the precipitants and try to change them. However, in those few selected cases in which treatment with medication may be helpful, it should only be used on a very short-term basis. Antihistamines are frequently used and few side effects other than sedation are reported. Diazepam has also been used but it should be remembered that it, because of its long half-life, accumulates and should only be increased every four to five days, if necessary.[63]

Anorexia Nervosa

In general, there is no sound scientific basis for the use of medication in anorexia nervosa. This mysterious illness, afflicting predominately girls in their early teenage years often requires hospitalization and intensive psychotherapeutic approaches including behavior modification, family therapy, individual psychotherapy and intravenous or tube feedings only if necessary. Dally and Sargent[64] describe their fortuitous discovery of short-term success with the use of chlorpromazine in addition to the usual psychotherapeutic treatment. They use rather large dosages of chlorpromazine starting at 300 mgs. a day and going over 1 gram a day. However, medication has not been effective in the long-term management of these patients and the risk-benefit ratio must carefully be considered in the use of such

high dosages for these conditions.

Summary

Drug treatment of children because of the complexities of the child and our relative ignorance of these complexities remains at the present time an art of empirically and systematically trying first one drug and then another till there is some amelioration of target symptoms. Drug treatment should almost never be the sole mode of intervention since drugs alone cannot provide new learning nor change the vital interactions between the child and his environment. The few guidelines there are for the drug treatment of children stress the following: do a complete history and physical on the child during which time the clinician attempts to maximize the rapport and the motivation for change; choose on the basis of the total clinical picture the class of drugs to be used; be familiar with one or two drugs in each class; start below the minimal therapeutic dosage and build up gradually till one sees amelioration of symptoms or side effects before switching to another drug or class of drugs; use the smallest effective dose with frequent drug holidays; stop the drug at the earliest time possible.

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The Maker

Examining a Few Myths About Prescribing.



Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand-name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to a reference product. As you know, there is substantial literature on this subject affecting many drugs, including such antibiotics as tetracycline and erythromycin. The record on drug recalls and court actions affirms strongly that there are differences among pharmaceutical companies and their products. Research-intensive companies have far better records than those that do no research and may practice minimum quality assurance.

MYTH: Industry favors only "expensive" brand names and denigrates all generics.

FACT: PMA companies make 90 to 95 percent of the drug supply, including, therefore, most of the generics. Drug nomenclature is not the important point; it's the competence of the manufacturer and the integrity of the product that count.

Matters.

MYTH: Generic options almost always exist.

FACT: About 55 percent of prescription drug expenditure is for single-source drugs. This means, of course, that for only 45 percent of such expenditure, is a generic prescribing option available.

MYTH: Generic prescriptions are filled with inexpensive generics, thus saving consumers large sums of money.

FACT: Market data show that you invariably prescribe—and pharmacists dispense—both brand and generically labeled products from known and trusted sources, in the best interest of patients. In most cases the patient receives a proven brand product. Savings from voluntary or mandated generic prescribing are grossly exaggerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

PMA

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Pharmacotherapy of Diarrhea

ROBERT G. PIETRUSKO, PHARM.D.

ABSTRACT

Most acute diarrheal conditions can be successfully managed by the avoidance of oral solids and ingestion of carbohydrate-electrolyte solutions. Opiates and synthetic compounds such as diphenoxylate and loperamide may reduce stool frequency in some patients but are associated with the risk of worsening and prolonging certain bacterial diarrheas and inflammatory bowel disease. They should be avoided in children since toxicity outweighs any potential benefit. Use of kaolin-pectin mixtures, anticholinergics, and Lactobacillus has been ineffective in the few adequately controlled double-blind trials that have been done. Cholestyramine may be useful for chronic diarrhea of various etiologies.

Recent discoveries of the underlying causes of diarrhea, such as *Cl. difficile* in antibiotic-induced pseudomembranous colitis and enterotoxigenic *E. coli*, in travelers' diarrhea are providing new insight into the prevention and treatment of diarrhea. Prostaglandins and vasoactive intestinal polypeptide (VIP) play a role in certain diarrheas.

Diarrhea is a common disease that has been experienced by most humans. As a part of ancient religious rituals, it was often induced by chemicals and herbs. Some degree of ritualism remains and today large sums are spent on the prevention and treatment of diarrhea. In 1975 alone, almost $95 million was spent in the United States on antidiarrheal medication.[1]

The term "diarrhea" is defined as passage of loose or liquid stools at an increased frequency. The final result is excess loss of water and electrolytes in the stool.[2] Studies of diarrhea have monitored stool weight and water content per 24 hours.[3,4] Under these circumstances, diarrhea in the adult has been defined as fecal excretion of greater than 300 g per day, as opposed to the "normal" excretion of 100 to 200 g per day. Increased fecal water content of several hundred milliliters above the average of 150 ml will contribute to diarrhea.[5]

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GASTROINTESTINAL PHYSIOLOGY

The human gastrointestinal tract effectively conserves water and electrolytes. In addition to an average oral intake of two liters of fluid per day, saliva and gastric secretion add three additional liters of fluid to the gastric contents. Isotonicity of ingested meals depends upon the foodstuffs ingested and will vary greatly. Isosmotic chyme moves rapidly into the duodenum whereas anisotonic material is delayed. In addition to the five liters entering the duodenum from the stomach, bile, pancreatic and intestinal secretions add another four liters of fluid every 24 hours.

Of the nine liters of fluid presented to the duodenum and jejunum, four liters are reabsorbed. Sodium and water are absorbed passively in the jejunum; the amount is determined by the degree of absorption of osmotic material (such as disaccharides and starch) contained in the chyme. Chloride is the major anion absorbed here. Potassium is absorbed passively, depending upon the electronegative potential.[2]

In the ileum and to a greater extent in the colon, active absorption of sodium occurs. Active sodium absoprtion in the small intestine may be related to glucose absorption.[6] Of the five liters presented to the ileum, 70% is reabsorbed. Chloride is actively reabsorbed and bicarbonate is excreted into the ileal lumen.

The colon is extremely efficient in conserving sodium and water. Of approximately 1.5 liters of fluid presented there, 90% is reabsorbed. As long as the rate of arrival is slow and there are no unabsorbed solutes present, the colon can absorb a maximum of 5700 ml of water and 816 mEq of sodium.[7] Much of the sodium is reabsorbed by active mechanisms.

Passive accumulation of potassium occurs in the colon to maintain ionic equilibrium and fecal concentration of potassium may approximate two to three times the plasma level. In addition to bicarbonate, 70% of the excreted fecal anions consist of organic salts such as proprionate, acetate, and butyrate.[8] Under normal circumstances, 150 ml of water, 5 mEq of sodium, 7 to 15 mEq of potassium, and 2 mEq of chloride are lost daily via the fecal route.[9]

Intestinal contents are mixed by the process of rhythmic segmentation which primarily involves contraction of circular smooth muscle. This material is sent aborally by peristaltic motion initiated by contraction of the longitudinal smooth muscles.[10,11] "Mass colonic movements" (the gastrocolic reflex)

Table 1

Normal Intestinal Fluid and Electrolyte Transport in 24 Hours

Site	Quantity of Fluid and Secretions Received	Amount Absorbed	Electrolyte Absorption		
			Na+	K+	Cl−
Duodenum and Jejunum	9 liters	4 liters	passive	passive	passive
Ileum	5 liters	3.5 liters	active	passive	active
Colon	1.5 liters	1.35 liters	active	passive accumulation	active

which occur shortly after meals are also important in peristalsis. Table 1 summarizes daily fluid and electrolyte transport.

Pathophysiology of Diarrhea

The mechanisms of diarrhea can be divided into three major categories: osmotic solute load, abnormalities of water and electrolyte transport, and altered intestinal motility. More than one mechanism may combine to produce diarrhea.

Osmotic factors include ingestion of poorly absorbed, osmotically active substances such as sorbitol and lactulose. Although not firmly documented, ingestion of a very large meal can produce diarrhea in some patients. Other examples of osmotic diarrhea include the postoperative "dumping syndrome," malabsorption of carbohydrates associated with disaccharidase deficiency, celiac sprue, and use of elemental diets. Osmotically active compounds induce excessive water influx into the jejunum. The severity of diarrhea in this condition depends upon the ability of the ileum and colon to absorb the excess fluid.[12] Osmotic diarrhea results predominantly in fluid loss rather than electrolyte depletion.[11]

Passive secretion is a result of increased mucosal permeability due to inflammation or damage to the intestinal mucosa. Inflammatory bowel disease; invasive strains of microorganisms such as Shigella, Salmonella, and *E. coli*; laxatives; and radiation enteritis are examples of factors that alter the mucosa causing passive secretion.[9,12,13] Active fluid and electrolyte secretion can result from the presence of toxin-producing bacteria *(V. Cholerae, Cl. perfringens, E. coli,* etc.), tumors that secrete activating hormones, and bile acids. Vasoactive intestinal polypeptide (VIP) and prostaglandins E and F have been implicated as the cause of the WDHA (watery diarrhea, hypokalemia, achlorhydria) syndrome.[14-19] In the Zollinger-Ellison syndrome, a pancreatic neoplasm produces a large quantity of gastrin that stimulates hypersecretion of gastric acid. High concentrations of hydrogen ions in the small intestine produce a secretory diarrhea by a direct effect.[20] Although the major alteration in water and electrolyte transport in diarrhea is probably hypersecretion, inhibition of absorption also plays a role.

The pathophysiology of intestinal motility disorders resulting in diarrhea are not clearly understood. When diarrhea occurs, the colon is relatively "quiet," with a minimal segmental contraction.[10] Small intestinal transit time is normal but transit time is shortened in the colon during a diarrheal episode.[21] Examples of disorders associated with altered colonic motility include diabetes, hyperthyroidism, scleroderma, short gut syndrome, carcinoid syndrome, and diarrhea induced by certain cathartics.

Diagnosis

Relevant questions to ask during history-taking in patients with diarrhea[4,22] include:

(1) How long has the diarrhea been present?
(2) Is rectal bleeding or melena (black stools) present?
(3) What medications (both prescription and over-the-counter products) are being taken?
(4) Are fever, weight loss or anorexia present?
(5) Has there been any recent foreign travel?
(6) Is the stool foul-smelling, light in color, or greasy?
(7) How frequent are the bowel movements?
(8) Is diarrhea related to milk intake?

The extent of volume depletion can be ascertained by such signs as tachycardia, postural hypotension, poor skin turgor, absence of axillary sweat, and elevated hematocrit or blood urea nitrogen concentrations. A stool specimen obtained at sigmoidoscopy should be examined for blood, fecal leukocytes, parasites, and fat.[23] Stool cultures should be obtained at sigmoidoscopy if Salmonella or Shigella are suspected. Depending upon initial findings, additional tests and procedures may be indicated. Metabolic disorders such as hyperthyroidism and diabetes should be ruled out.

Treatment

The approach to managing diarrhea can be divided into three basic categories: supportive, symptomatic, and specific.

Supportive Therapy

Supportive therapy consists of replacing fluid and electrolyte losses.[6,24] When intravenous fluids are used in replacement therapy, the specific composi-

Table 2

Sodium and Potassium Content of Oral Liquids*

Liquid	mEq/L Sodium	Potassium
Apple Juice	1.7	26
Coca Cola	1	0.4
Gatorade	23	2.5
Ginger Ale	3.5	0.1
Jello (half strength)	15	0.15
Lytren	25	25
Orange Juice	0.2	49
Pedialyte	30	20
Pepsi	0	0.6
7-Up	5	0.3

*The electrolyte values for some of these products may vary slightly depending upon the electrolyte content of local water supplies.

tion can be adjusted to meet the needs of the patient by close clinical monitoring. The following oral solution is recommended by the World Health Organization for treating diarrhea in all age groups: 2% glucose in a solution containing sodium 90 mEq/L, chloride 75 mEq/L, potassium 15 mEq/L, and bicarbonate 30 mEq/L.[25] Although possibly less efficient, others have proposed utilizing sucrose instead of glucose in the above solution because of its greater availability and lower cost.[26-28] These carbohydrate-electrolyte solutions are most useful for cholera and enteropathogenic *E. coli* diarrheas in adults and children older than two years of age.

In children, especially under the age of two, "standard" oral solutions high in sodium concentration may induce hypernatremia.[29] This can be a particular problem in viral-induced diarrhea when fecal sodium excretion is reduced.[30] Use of solutions with sodium concentrations of 50 mEq/L in children under four years of age reduces the risk of hypernatremia.[25] Most cases of acute childhood diarrhea are managed by stopping oral solid feedings and administering clear liquids such as "decarbonated" soft drinks, fruit juices, diluted flavored gelatin, or commercial products such as Pedialyte® and Lytren® .[31]

The use of skim milk or bouillon can produce hypernatremia and should be avoided. Unflavored gelatin and Kool-Aid® are inadequate replacement solutions since they are very low in sodium and potassium. The electrolyte concentration of various products are listed in Table 2. Clear liquids are maintained for 24 to 48 hours, and then followed by a bland diet. Occasionally, lactose intolerance develops; in infants, a lactose-free formula such as Isomil® or Prosobee® should be utilized for two to six weeks as a therapeutic trial.

Symptomatic Therapy

Symptomatic therapy of diarrhea involves the use of drugs that do not alter the underlying pathophysiology or correct the electrolyte and fluid loss. They may reduce the number of bowel movements or improve the consistency of the stool but there is no evidence that their use actually benefits the patient.[32]

Opiates. The principal opium alkaloids that affect gastrointestinal smooth muscle function are morphine and codeine. These drugs and diphenoxylate, a synthetic antidiarrheal drug, increase circular smooth muscle tone of the intestine,[33] which leads to nonpropulsive rhythmic contractions.[34]

The action of various galenical opium preparations used to treat diarrhea is primarily due to their morphine content. Tincture of opium is a hydroalcoholic solution that is adjusted to contain 1% morphine. The average dose is 0.6 to 1.5 ml, which is equivalent to 6 to 15 mg of morphine. Paregoric (camphorated opium tincture) contains the equivalent of 2 mg of morphine in each 5 ml dose. Codeine is used in an average dose of 15 mg four times a day, although doses can range as high as 240 mg daily.[35] Two cases of paradoxical diarrhea have been reported when these products were withdrawn from patients treated for chronic diarrhea.[36]

Synthetic Antidiarrheals. Agents with gastrointestinal properties similar to the opiates but with less addictive potential are diphenoxylate and loperamide.[37] To minimize abuse of diphenoxylate, a subtherapeutic dose of 0.025 mg atropine has been added to Lomotil® , the commercial preparation. Diphenoxylate is structurally related to meperidine. In terms of therapeutic equivalence, 15 mg of diphenoxylate is equal to about 45 mg of codeine.[38] The daily recommended dose is 5 mg (two tablets) four times a day. Lomotil should be avoided in patients with chronic liver disease, since hepatic coma may occur.[39] Children under the age of two are extremely sensitive to the depressant effects of diphenoxylate; therefore, the drug is contraindicated in this age group.[40] Ingestion of as little as six tablets has resulted in the death of a two year-old child. Pronounced symptoms of central nervous system depression may develop in children taking only one to five tablets.[41] Early signs of intoxication may resemble atropinism in some cases.[42] Hospital admission is required in all such cases since effects can be delayed up to 12 hours after ingestion.[43] Gastric lavage should also be performed since tablets can be recovered up to 72 hours after ingestion, due to delayed intestinal motility. Greater than 90% of diphenoxylate is absorbed with peak plasma levels occurring within two to three hours. The serum half-life of the parent compound is 2.5 hours.[44] Diphenoxylate is metabolized via hydrolysis to diphenoxylic acid which is also active.[45] This metabolite is excreted into the bile and undergoes enterohepatic circulation, thus prolonging the activity of the drug. Less than one percent of diphenoxylate is excreted unchanged in the urine.

Loperamide (Imodium®) is a recently introduced synthetic antidiarrheal compound which is similar in structure to haloperidol, a butyrophenone antipsychotic agent. The recommended dosage for acute and chronic diarrhea is 4 mg initially, followed by 2 mg as needed to a maximum of 16 mg per day. To

TABLE 3

STUDIES OF THE ANTIDIARRHEAL EFFICACY OF DIPHENOXYLATE AND LOPERAMIDE

Reference	Number of Patients	Type of Diarrhea	Agents Tested	Placebo	Double-Blind	Statistics[a]	Parameters
49	213	acute	loperamide, diphenoxylate, clioquinol	+	+	L vs D,Cl: sig L vs P: sig D vs P: N.S. Cl vs P: N.S.	Time for first occurrence of unformed stool after a single dose
50	40	chronic	diphenoxylate, paregoric	+	+	N.D.	Stool frequency and consistency
39	81	chronic	diphenoxylate	–	–	N.D.	Stool frequency
51	23	chronic	diphenoxylate, codeine	+	+	D vs P: sig C vs P: sig D vs C: N.S.	Stool frequency and consistency
52	340	acute	loperamide, diphenoxylate	–	+	L vs D: sig	Stool frequency and consistency
53	10	chronic	loperamide	+	+	L vs P: sig	Stool frequency and consistency
54	614	acute	loperamide, diphenoxylate	–	+	L vs D: sig	Interval between doses and number of doses
55	19	chronic	loperamide	+	+	N.D.	Stool frequency and consistency
56	244	acute	diphenoxylate, clioquinol	–	+	D vs Cl: N.S.	Stool frequency and consistency
57	81	acute	diphenoxylate, clioquinol	–	+	D vs Cl: N.S.	Stool frequency and consistency
58	50	acute	diphenoxylate	+	+	N.D.	Stool frequency, State of hydration, Duration of illness
59	83	acute	loperamide, diphenoxylate	–	–	L vs D: N.S.	Time for first occurrence of unformed stool after repeated doses
60	161	acute	diphenoxylate-neomycin, kaolin-neomycin-sulfa	–	–	D-N vs K-N-S: sig	Stool frequency and consistency
61	23	chronic	loperamide, diphenoxylate	–	+	L vs D: sig	Stool frequency and consistency
62	80	acute	diphenoxylate, kaolin-pectin	+	+	D vs P: N.S. K-P vs P: N.S.	Stool frequency, consistency, and water content
63	20	chronic	loperamide	+	+	L vs P: sig	Mean daily ileostomy output
64	10	chronic	diphenoxylate	–	–	N.D.	Stool frequency and consistency

a: C = codeine, Cl = clioquinol, D = diphenoxylate, D-N = diphenoxylate-neomycin, K-P = kaolin-pectin, K-N-S = kaolin-neomycin-sulfa, L = loperamide, N.D. = statistics were not done, N.S. = not statistically significant, P = placebo, Sig = statistically significant difference

date, there have been no reports of severe central nervous system depression due to accidental ingestion of this product. It is claimed that loperamide has a more rapid and longer-lasting effect than diphenoxylate.[44] Peak leavels of loperamide occur within four hours, with a half-life of 7 to 15 hours.[46] Although this drug is superior to placebo in several studies of symptomatic therapy for acute and chronic diarrhea, more well-controlled studies are needed to determine if loperamide is more effective than diphenoxylate.

All of the above-mentioned antidiarrheals should be avoided in children since fluid losses may be masked, toxicity is more pronounced, and bacterial diarrheas may become more severe and prolonged.[42,47,48] Use in adults may reduce the inconvenience and discomfort of frequent visits to the toilet but is associated with the risk of increasing toxicity of a bacterial diarrhea, if present. Patients with ulcerative colitis may develop toxic megacolon. These drugs should not be used in patients with partial bowel obstruction. Table 3 describes studies of diphenoxylate and loperamide.

Anticholinergics. Atropine, tincture of belladonna, propantheline (Pro-Banthine®) and numerous other anticholinergic products are often used in treating diarrhea. However, no controlled studies on

their effectiveness have been published. A decrease in gastrointestinal motility and tone is seen only with doses sufficient to cause side effects.[34] The only possible benefit is to decrease intestinal spasm and pain.[32] In one study, neither tincture of belladonna nor propantheline had any effect on diarrhea in patients with ileostomies.[35] Doses commonly utilized are as follows: tincture of belladonna, 0.6 ml; atropine sulfate, 0.6 to 1.0 mg; and propantheline, 15 mg.

Adsorbents. Some of these products have been used in the treatment of diarrhea since ancient times, but well-controlled clinical trials are lacking.[65] Kaolin is a native hydrated aluminum silicate.[5] The supposed ability of this clay to adsorb large numbers of bacteria and toxins, such as *E. coli, Cl. welchi,* and *L. acidophilus*, or toxin produced by Shigella and *E. coli*, has not been established.[66,67] Pectin is a polyuronic polymer consisting of purified carbohydrate extracted from citrus fruit or apple pumice.[5] Up to 90% of this drug is decomposed in the gastrointestinal tract.[68] A decrease in the pH of the intestine due to production of galacturonic acid and the adsorbent properties of pectin have been analyzed, but the effect of pectin in diarrhea is unknown.[69]

Kaopectate® is a popular proprietary product which contains 25% kaolin and 1% pectin. Its effectiveness is not proven. In one study, the stools appeared to be more formed with this product, but there was no decrease in stool frequency or fecal weight and water content.[62] This may produce a misleading and potentially dangerous situation when evaluating fluid losses.[38] In addition to its questionable efficacy, the absorption of digoxin and lincomycin may be impaired if given concurrently with Kaopectate.[70,71] The recommended dose is 60 to 120 ml.

Cholestyramine is an anionic exchange resin which possesses a strong affinity for acidic materials, including bile acids. This drug has been used to treat antibiotic-induced colitis as well as chronic diarrhea associated with diabetes mellitus, abdominal irradiation, vagotomy, ileal resection, and intractable infantile diarrhea.[72] However, tropical diarrhea plaguing United States troops in Vietnam did not respond to cholestyramine.[73] The usual dosage is 4 g two to four times a day. Cholestyramine powder must be diluted with a liquid such as fruit juice or added to applesauce, and administered at least two hours before ingestion of meals and other medications since it can bind with fat-soluble vitamins and many other drugs.[74] Colestipol, another anionic exchange resin that was recently introduced, may also be useful in treating certain diarrheas.

Lactobacillus. For the treatment of diarrhea due to intestinal overgrowth of enteric pathogens, Lactobacillus-containing products (Bacid® , Lactinex® , yogurt) have been tried in an effort to restore the normal flora. Anecdotal reports suggest that they lessen diarrhea,[75] but there are no well-controlled studies documenting their effectiveness. Lactobacillus was superior to a neomycin-containing product, although the use of an antibiotic in the control group may have worsened the diarrhea.[76] In a double-blind controlled trial, 94 children less than three years of age with acute diarrhea were given Lactobacillus or placebo.[77] There was no statistically significant difference between the two groups in the number and size of stools passed. The average dose is four to eight capsules per day or 1 g of powder four times a day.

Specific Therapy

Specific therapy is aimed at treating the underlying condition or blocking the cellular mechanisms of fluid and electrolyte loss. Antibiotics are examples of specific therapy which may be effective in treating some bacterial diarrheas. Other examples include: surgery, treatment of metabolic disorders, replacing of pancreatic enzymes, and discontinuation of diarrhea-causing drugs.

Prostaglandin antagonists, such as aspirin and indomethacin, and other compounds, such as propranolol, show promise in treating diarrheas by preventing the activation of adenylate cyclase.[78,79] Corticosteroids may be beneficial in secretory diarrheas by increasing Na, K-ATPase activity and stimulating an independent absorptive process.[80] The association of elevated levels of vasoactive intestinal polypeptide (VIP) with certain types of diarrhea has stimulated efforts to identify VIP antagonists. Dihydroergotamine, an alpha adrenergic blocking agent, rapidly improved diarrhea of various etiologies in 121 out of 123 patients.[81]

Acute Diarrhea

The causative factor in acute diarrhea is not known in most cases,[82] and it is not known whether most are bacterial or viral in nature.[5,83] According to one hypothesis, microorganisms contained in normal bowel flora may be responsible for acute diarrhea.[82] Viruses (particularly rotavirus) are the generally accepted etiological agents in most cases of seasonal gastroenteritis in children.[84] The role of stress in producing diarrhea is mainly conjectural at this time. Dietary indiscretion and medication, especially antibiotics and laxatives, also are possible causes of acute diarrhea.

Diarrhea Caused by Microorganisms

Travelers' diarrhea. With the increased mobility of the world population, much attention has been focused on "travelers' diarrhea." People obviously wish to avoid debilitating diarrhea while on vacation or attending a convention. The traveler may experience up to ten to twenty episodes a day accompanied by abdominal cramps, chills, fever, nausea and vomiting.[85] Recent evidence suggests that up to 70% of these cases may be caused by pathogenic strains of *E. coli.*[86] High attack rates are associated with eating salads containing raw vegetables.[87] Various strains of *E. coli* can produce heat-labile (LT) and heat stable (ST) enterotoxins, but current laboratory tests for enterotoxins are not suitable for routine use.[88,89] Travelers' diarrhea is a

self-limited illness, usually lasting from several days to one to two weeks. The diagnosis can only be made after several stool examinations for ova and parasites and stool cultures have excluded other infectious diseases, e.g., shigellosis, salmonellosis, amebiasis, giardiasis (discussed below).

Obviously, the best method of treatment is prevention. The number of organisms ingested is the major determinant of infectivity. Gastric acidity provides a substantial barrier to enteric infections such as *Vibrio cholerae*. Use of agents which increase alkalinity such as antacids and cimetidine favors the survival of ingested organisms.[90] Avoidance of these drugs and of raw foods and local drinking water should be helpful. Prophylactic antibiotics afford some protection. British travelers utilizing Streptotriad (a streptomycin-sulfa mixture) had less diarrhea compared to travelers given a placebo.[91] As a part of the same study, a neomycin-sulfa compound was beneficial in reducing symptoms but not diarrhea. No attempt was made to isolate organisms or to categorize how effective each therapy was in individual countries. Prophylactic use of phthalylsulfathiazole, 2 g daily, or neomycin sulfate, 1 g daily, by travelers to Mexico was more effective than placebo;[92] 473 students were enrolled in this program. Moderate to severe diarrhea occurred in 5.1% and 6.6% of the neomycin and sulfa groups respectively, compared to 17.3% in the placebo group ($p < 0.01$). In a double-blind controlled study, Peace Corps volunteers in Kenya who took 100 mg of doxycycline daily had a reduction of 45 to 55% in the incidence of diarrhea.[93] The protection afforded by this tetracycline derivative seemed to last for at least one week after it was discontinued. The routine usage of prophylactic antibiotics always raises the question of development of resistant bacterial strains.[94-96]

Although never documented as effective, iodochlorhydroxyquin has been frequently prescribed for prophylaxis.[97] After drug-induced subacute myelo-optico-neuropathy was documented, its use was prohibited in the United States.[98] The problems associated with this product have not disappeared since it is readily available without a prescription in many foreign countries. Other names of iodochlorhydroxyquin include clioquinol, Amebil®, Bactol®, and Vioform®.[99,100]

Current research is directed at the development of a vaccine, possibly the safest and most effective way of preventing bacterial diarrhea.[93,101]

Many remedies have been advocated for suppressing travelers' diarrhea, once it has begun. Antimotility drugs, such as opiate derivatives and anticholinergics, may prolong or enhance the severity of the infectious process by interfering with normal defense mechanisms.[102-104] Normal intestinal motility may also play a role in absorption of fluid and electrolytes. Judicious use of diphenoxylate may provide symptomatic relief of severe abdominal cramping. Antimicrobial drugs, such as sulfathalidine, colistin, neomycin or tetracycline, are not effective in the treatment of travelers' diarrhea[105,106] possibly because the organism is needed for the initiation but not the perpetuation of diarrhea. No well-controlled studies can substantiate the effectiveness of kaolin or pectin. Lactobacillus is ineffective for preventing or modifying this condition.[107] Pepto-Bismol decreases the number of unformed stools, and subjective complaints of nausea and abdominal cramping.[108] The active ingredient in this product is bismuth subsalicylate. Its possible efficacy may be explained by the inhibitory effect of salicylate on prostaglandins.[109] Prostaglandins have been implicated in the mediation of fluid production induced by the microorganism or its enterotoxin.

Fluid and electrolyte replacement remains the most important aspect of treatment.[102]

Cholera. The microorganism *Vibrio cholerae* liberates an endotoxin into the intestinal lumen which causes massive secretion of fluid and electrolytes.[110] Addition of glucose to oral fluid and electrolyte replacement solutions facilitates sodium absorption and can be a life-saving factor in many underdeveloped countries where cholera is prevalent.[6,24] Antimotility drugs are of no value. Although early reports suggest that kaolin may be useful, in a recent controlled trial the addition of kaolin to the standard glucose-electrolyte solution did not improve outcome.[111] Tetracycline may be of some benefit in shortening the duration of the diarrheal attack.[112] The anti-prostaglandin activity of indomethacin is currently being evaluated in the treatment of cholera.[105,113]

Giardiasis. Diarrhea caused by *Giardia lamblia* can be effectively treated with quinacrine hydrochloride (Atabrine®), 100 mg, or metronidazole (Flagyl®), 250 mg, three times daily for seven to ten days.[114,115] Giardia is frequently difficult to detect in stool examinations, with negative results in over 50% of cases. Duodenal aspiration and small bowel biopsy is usually diagnostic when stool examinations are negative. Transmission usually occurs via contaminated water supplies.[116]

Shigellosis. Shigella and Salmonella are invasive microorganisms that do not characteristically produce endotoxins. Invasion of the distal colon and rectum produces symptoms of urgency, tenesmus, and passage of blood and mucus.[117] Most cases of Shigella seen in the United States need not be treated since they are mild and self-limited.[110] Which isolated strains of Shigella require antibiotic therapy is not established. Ampicillin is generally regarded as the drug of choice if therapy is indicated.[118] Amoxicillin is less effective.[119] Other recommended drugs are trimethoprim-sulfamethoxazole (Bactrim®, Septra®) and a single 2.5 g dose of tetracycline.[120-122]

Salmonellosis. Antibiotic therapy is contraindicated in the treatment of Salmonella unless the typhosa strain is isolated or if systemic infection has occurred. Use of antibiotics not only fails to cure the disease but also may prolong the post-convalescent excretion of Salmonella.[123] Such therapy may also cause "in vitro" acquisition of antibiotic resistance.

Antimotility drugs should be avoided if diarrhea is

due to invasive organisms. These medications may enhance epithelial penetration and local multiplication of the infecting agent by inhibiting intestinal motility, thereby decreasing the excretion of bacteria and toxins. In a study of twenty-five men with induced Shigellosis, those who were treated with diphenoxylate had fever and toxemia two to three times longer than the untreated group.[104] Clinical reports and animal data indicate that antimotility agents also worsen and prolong Salmonellosis.[103,124]

Amebiasis. Symptoms of enteral infection due to the protozoa *Entamoeba histolytica* can vary from mild diarrhea to fulminant dysentery. When intestinal amebiasis is suspected, proctosigmoidoscopy with rectal biopsy should be performed since stool specimens are frequently negative. Serological tests may also be helpful. For treatment of symptomatic intestinal amebiasis, the drug of choice is metronidazole 750 mg three times a day for five to ten days.[125] Cysts can be eradicated with either diiodohydroxyquin 650 mg three times a day for three weeks or the investigational drug diloxanide furoate (Furamide), 500 mg three times a day for ten days.[126]

Drug-Induced Diarrhea

Almost any drug, including placebo, can cause diarrhea. It is a frequent side effect of colchicine, magnesium hydroxide-containing antacids, laxatives, lactulose, guanethidine, quinidine, certain antibiotics, and digitalis. Most of these drugs produce reversible diarrhea that remits upon discontinuation. Some antibiotics may cause a more severe form of diarrhea that can be life-threatening if not managed properly. Pseudomembranous colitis has been associated with the use of penicillin G, tetracycline, ampicillin, cephalexin, chloramphenicol, trimethoprim-sulfamethoxazole, lincomycin and clindamycin.[127-133] Clindamycin is most frequently implicated, leading to the descriptive term "clindamycin colitis." The reported frequency of clindamycin-related pseudomembranous colitis ranges from one in twenty to one in 50,000 to 100,000 recipients.[130-133] Onset of colitis may occur up to two weeks after the drug is stopped and is quite rare in children.[134,135] Diagnosis is made by the presence of pseudomembranes composed of mucin, fibrin, white blood cells, and discarded epithelial cells. They are attached to a necrotic mucosal surface of the colon and appear as exudative whitish plaques at proctosigmoidoscopy.[136]

The principal mode of therapy is fluid and electrolyte replacement as well as discontinuation of the drug. An important recent observation is that clindamycin colitis is due to the toxin-producing *Clostridium difficile.*[137-142] Early evidence suggests that vancomycin may be the drug of choice.[143-146] Many cases of staphylococcal enterocolitis may actually have been due to *Cl. difficile* and were "serendipitously" treated with vancomycin.[147] Tetracycline was successful in treating three patients with antibiotic-induced diarrhea.[148] However, this antibiotic is probably not the drug of choice since some isolated strains of *Cl. difficile* are resistant.[140] Metronidazole may also be useful.[127] Diphenoxylate and other antimotility drugs have been used without much success,[137,148,149] and may actually enhance toxicity.[133,150,151] A double-blind prospective study in healthy volunteers demonstrated a higher incidence of diarrhea when diphenoxylate was administered with lincomycin than when placebo was given.[152] Although interpretation of these data is controversial,[153] antimotility drugs are at best of questionable efficacy and may prolong and increase the severity of the colitis.[154]

Cholestyramine was successfully used in three cases of pseudomembranous colitis.[155,156] Although further study is necessary, the ability of this resin to adsorb the cytopathic toxin "in vitro" may be therapeutically useful.[157] The efficacy of corticosteroids is not established.

Table 4

Treatment of Some Specific Chronic Diarrheas

Condition	*Treatment*
Bacterial Overgrowth Syndrome	antibiotics
Extensive Bowel Resection	MCT (medium-chain triglyceride) oil, reduced dietary fat
Inflammatory Bowel Disease	sulfasalazine, steroids
Irritable Bowel Syndrome	increase dietary fiber, anti-depressants?, anticholinergics?
Lactase Deficiency	avoid dietary lactose (milk and milk products)
Nontropical Sprue	gluten-free diet
Pancreatic Insufficiency	pancreatic enzyme supplementation

Viral Diarrhea

Diarrhea due to viral infections is quite common and usually of short duration.[84] Treatment consists mainly of fluid and electrolyte replacement. Although viral diarrhea may transiently impair carbohydrate metabolism, oral sugar-electrolyte solutions are nevertheless useful.[28] Antimotility drugs, when they are effective, decrease the number of stools and relieve cramps, but they do not alter any underlying pathology or prevent fluid and electrolyte loss. In a study of eighty children with acute nonspecific diarrhea, neither diphenoxylate nor kaolin-pectin suspension had any effect on frequency of bowel movement or stool weight and water content.[62] Unnecessary drug prescribing for children with diarrhea should be avoided.

Chronic Diarrhea

Definitive rather than symptomatic treatment of chronic diarrhea requires identification of the

underlying cause (Table 4), if possible. Prolonged use of narcotic derivatives that may lead to dependence should be avoided. For irritable bowel syndrome, anticholinergic agents have been used extensively, although there is no reliable evidence supporting their efficacy.[158,159] These agents shorten the duration and reduce abnormal myoelectric and motor responses to a meal in the irritable bowel syndrome, but their benefit in controlling diarrhea is unknown.[160] Narcotic-type antidiarrheal agents, aluminum salts, tricyclic antidepressants, high fiber diets and cholestyramine may occasionally be of some benefit.[161]

Some patients with inflammatory bowel disease have diarrhea even after treatment with sulfasalazine and steroids. Judicious use of opiates and anticholinergics may provide symptomatic relief of abdominal cramps and diarrhea in regional enteritis.[162] Use of these drugs in ulcerative colitis should be avoided if possible since toxic megacolon may result.[163]

After ileal resection, most patients develop bile acid malabsorption. Passage of the unabsorbed bile acids into the colon stimulates secretion of sodium and water. Administration of cholestyramine to patients with less than 100 cm of distal ileum resected significantly decreases fecal weight and stool frequency as well as sodium excretion.[164,165] In a study undertaken to determine the effects of symptomatic therapy on ileal contents,[35] only bismuth subgallate significantly reduced normal ileal excreta. Codeine sulfate, tincture of opium, and diphenoxylate were effective in some patients but the sample size (average of three tested with each drug) was too small for meaningful conclusions. Propantheline, tincture of belladonna, and kaolin-pectin had no obvious beneficial effect in decreasing ileal output. In a double-blind crossover study of twenty patients with ileostomies, loperamide was significantly more effective than placebo in reducing fecal weight.[166] Both loperamide and diphenoxylate can provide symptomatic relief in many patients with chronic diarrhea of various etiologies.[55,61]

Chronic nonspecific diarrhea is a relatively benign disease that occurs in children from six months to three years of age. A change in diet may be the only necessary treatment.[167] Milk intolerance (lactase deficiency and less commonly, milk sensitivity) should be ruled out. For intractable infantile diarrheas, cholestyramine, elemental diets and hyperalimentation have appreciably reduced morbidity and mortality.[168-170]

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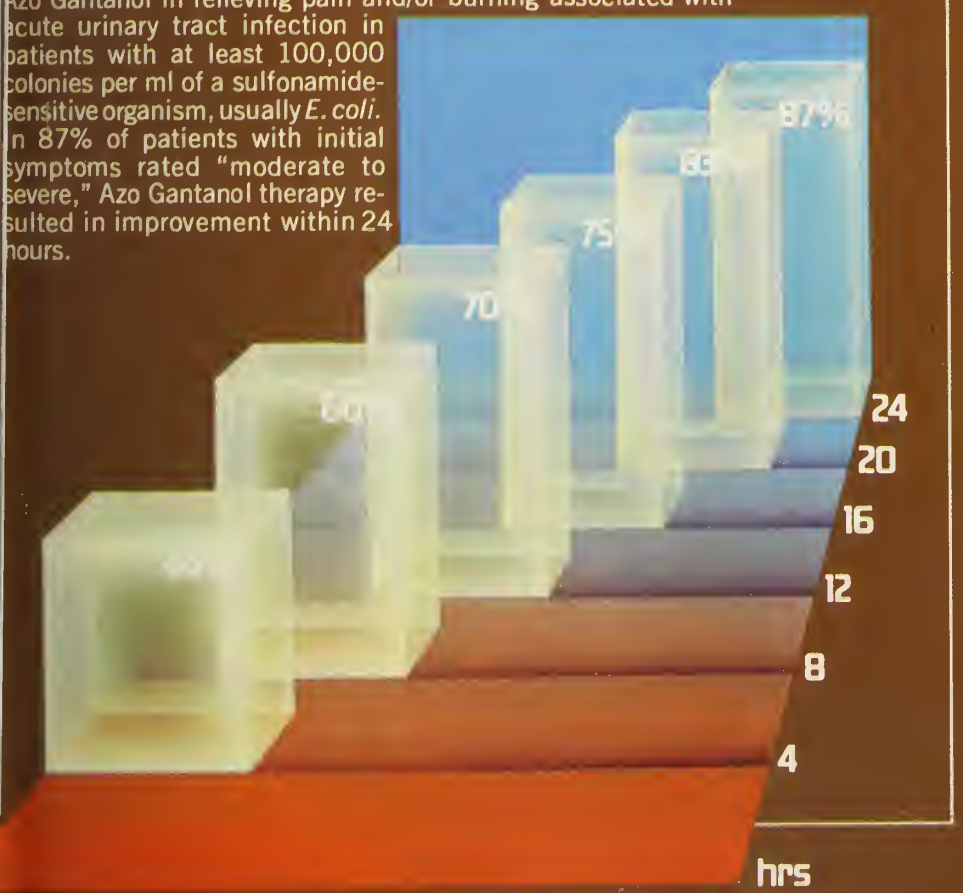
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mportant data on the pain of acute cystitis:

n 87% of patients studied [303 of 349], Azo Gantanol® reduced pain and/or burning within 24 hours*

A controlled, multicenter study assessed the efficacy of Azo Gantanol in relieving pain and/or burning associated with acute urinary tract infection in patients with at least 100,000 colonies per ml of a sulfonamide-sensitive organism, usually *E. coli*. In 87% of patients with initial symptoms rated "moderate to severe," Azo Gantanol therapy resulted in improvement within 24 hours.



Before prescribing, please consult complete prod uct information, a summary of which follows:

Indications: In adults, urinary tract infections complicated by pain (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis,* and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period; because Azo Gantanol contains phenazopyridine hydrochloride it is contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with G. disturbances.

Warnings: Safety during pregnancy not established. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, Stevens-Johnson syndrome, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *G.I. reactions* (nausea, emesis, abdominal pain, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Azo Gantanol is intended for the acute, painful phase of urinary tract infections. *Usual adult dosage:* 2 Gm (4 tabs) initially, then 1 Gm (2 tabs) B.I.D. for up to 3 days. If pain persists, causes other than infection should be sought. After relief of pain has been obtained, continued treatment with Gantanol (sulfamethoxazole) may be considered.

NOTE: Patients should be told that the orange-red dye (phenazopyridine HCl) will color the urine.

Supplied: Tablets, red, film-coated, each containing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 500.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche I
Nutley, New Jersey 07110

Fast pain relief plus effective antibacterial action

Azo Gantanol®

Each tablet contains 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl.

for the pain

for the pathogens



A reminder

ZYLOPRIM®

(allopurinol)

100 and 300 mg scored Tablets

- inhibits uric acid formation
- helps prevent urate crystal depositions in synovia
- reduces risk of uric acid lithiasis

INDICATIONS AND USE: This is not an innocuous drug and strict attention should be given to the indications for its use. Pending further investigation, its use in other hyperuricemic states is not indicated at this time.

Zyloprim® (allopurinol) is intended for:

1. treatment of gout, either primary, or secondary to the hyperuricemia associated with blood dyscrasias and their therapy;
2. treatment of primary or secondary uric acid nephropathy, with or without accompanying symptoms of gout;
3. treatment of patients with recurrent uric acid stone formation;
4. prophylactic treatment to prevent tissue urate deposition, renal calculi, or uric acid nephropathy in patients with leukemias, lymphomas and malignancies who are receiving cancer chemotherapy with its resultant elevating effect on serum uric acid levels.

CONTRAINDICATIONS: Use in children with the exception of those with hyperuricemia secondary to malignancy. The drug should not be employed in nursing mothers.

Patients who have developed a severe reaction to Zyloprim should not be restarted on the drug.

WARNINGS: ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme) and very rarely a generalized vasculitis which may lead to irreversible hepatotoxicity and death.

A few cases of reversible clinical hepatotoxicity have been noted and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. Accordingly, periodic liver function tests should be performed during the early stages of therapy, particularly in patients with pre-existing liver disease.

Patients should be alerted to the need for due precautions when engaging in activities where alertness is mandatory.

Nevertheless, iron salts should not be given simultaneously with Zyloprim. This drug should not be administered to immediate relatives of patients with idiopathic hemochromatosis.

In patients receiving Purinethol® (mercaptopurine) or Imuran® (azathioprine), the concomitant administration of 300-600 mg of Zyloprim per day will require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of Purinethol or Imuran should be made on the basis of therapeutic response and any toxic effects.

Usage in Pregnancy and Women of Childbearing Age. Zyloprim® (allopurinol) should be used in pregnant women or women of childbearing age only if the potential benefits to the patient are weighed against the possible risk to the fetus.

PRECAUTIONS: Some investigators have reported an increase in acute attacks of gout during the early stages of allopurinol administration, even when normal or subnormal serum uric acid levels have been attained.

It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. This interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

A fluid intake sufficient to yield a daily urinary output of at least 2 liters and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable to (1) avoid the theoretic possibility of formation of xanthine calculi under the influence of Zyloprim therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Patients with impaired renal function require less drug and should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in renal function appear.

In patients with severely impaired renal function, or decreased urate clearance, the half-life of oxipurinol in the plasma is greatly prolonged. Therefore, a dose of 100 mg per day or 300 mg twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels. Such patients should be treated with the lowest effective dose, in order to minimize side effects.

Mild reticulocytosis has appeared in some patients.

As with all new agents, periodic determination of liver and kidney function and complete blood counts should be performed especially during the first few months of therapy.

ADVERSE REACTIONS:

Dermatologic: Because in some instances skin rash has been followed by severe hypersensitivity reactions, it is recommended that therapy be discontinued at the first sign of rash or other adverse reaction (see WARNINGS). Skin rash, usually maculopapular, is the adverse reaction most commonly reported.
Exfoliative, urticarial and purpuric lesions, Stevens-Johnson syndrome (erythema multiforme) and toxic epidermal necrolysis have also been reported.
A few cases of alopecia with and without accompanying dermatitis have been reported.
In some patients with a rash, restarting Zyloprim (allopurinol) therapy at lower doses has been accomplished without untoward incident.

Gastrointestinal: Nausea, vomiting, diarrhea, and intermittent abdominal pain have been reported.

Vascular: There have been rare instances of a generalized hypersensitivity vasculitis or necrotizing angiitis which have led to irreversible hepatotoxicity and death.

Hematopoietic: Agranulocytosis, anemia, aplastic anemia, bone marrow depression, leukopenia, pancytopenia and thrombocytopenia have been reported in patients, most of whom received concomitant drugs with potential for causing these reactions. Zyloprim® (allopurinol) has been neither implicated nor excluded as a cause of these reactions.

Neurologic: There have been a few reports of peripheral neuritis occurring while patients were taking Zyloprim. Drowsiness has also been reported in a few patients.

Ophthalmic: There have been a few reports of cataracts found in patients receiving Zyloprim. It is not known if the cataracts predated the Zyloprim therapy. "Toxic" cataracts were reported in one patient who also received an anti-inflammatory agent; again, the time of onset is unknown. In a group of patients followed by Gutman and Yü for up to five years on Zyloprim therapy, no evidence of ophthalmologic effect attributable to Zyloprim was reported.

Drug Idiosyncrasy: Symptoms suggestive of drug idiosyncrasy have been reported in a few patients. This was characterized by fever, chills, leukopenia or leukocytosis, eosinophilia, arthralgias, skin rash, pruritus, nausea and vomiting.

OVERDOSAGE: Massive overdosing, or acute poisoning, by Zyloprim has not been reported.

HOW SUPPLIED: 100 mg (white) scored tablets, bottles of 100 and 1000; 300 mg (peach) scored tablets, bottles of 30, 100 and 500. Unit dose packs for each strength also available.

Complete information available from your local B. W. Co. Representative or from Professional Services Department PML.

U.S. Patent No. 3,624,205 (Use Patent)

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709



Does it influence your choice of a peripheral/cerebral vasodilator*?

- Vasodilan—compatible with coexisting diseases
- Vasodilan—compatible with concomitant therapy
- Vasodilan—compatible with your total regimen for vascular insufficiency

*Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Vasodilan injection, isoxsuprine HCl, 5 mg., per ml.

Dosage and Administration: Oral: 10 to 20 mg., three or four times daily.

Intramuscular: 5 to 10 mg (1 or 2 ml.) two or three times daily. Intramuscular administration may be used initially in severe or acute conditions.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Parenteral administration is not recommended in the presence of hypotension or tachycardia.

Intravenous administration should not be given because of increased likelihood of side effects.

Adverse Reactions: On rare occasions oral administration of the drug has been associated in time with the occurrence of hypotension, tachycardia, nausea, vomiting, dizziness, abdominal distress, and severe rash. If rash appears the drug should be discontinued.

Although available evidence suggests a temporal association of these reactions with isoxsuprine, a causal relationship can be neither confirmed nor refuted.

Administration of single dose of 10 mg. intramuscularly may result in hypotension and tachycardia. These symptoms are more pronounced in higher doses. For these reasons single intramuscular doses exceeding 10 mg. are not recommended. Repeated administration of 5 to 10 mg. intramuscularly at suitable intervals may be employed.

Supplied: Tablets, 10 mg., bottles of 100, 1000, 5000 and Unit Dose; Tablets, 20 mg., bottles of 100, 500, 1000, 5000 and Unit Dose; Injection, 10 mg. per 2 ml. ampul, box of six 2 ml. ampuls.

U.S. Pat. No. 3,056,836

VASODILAN®

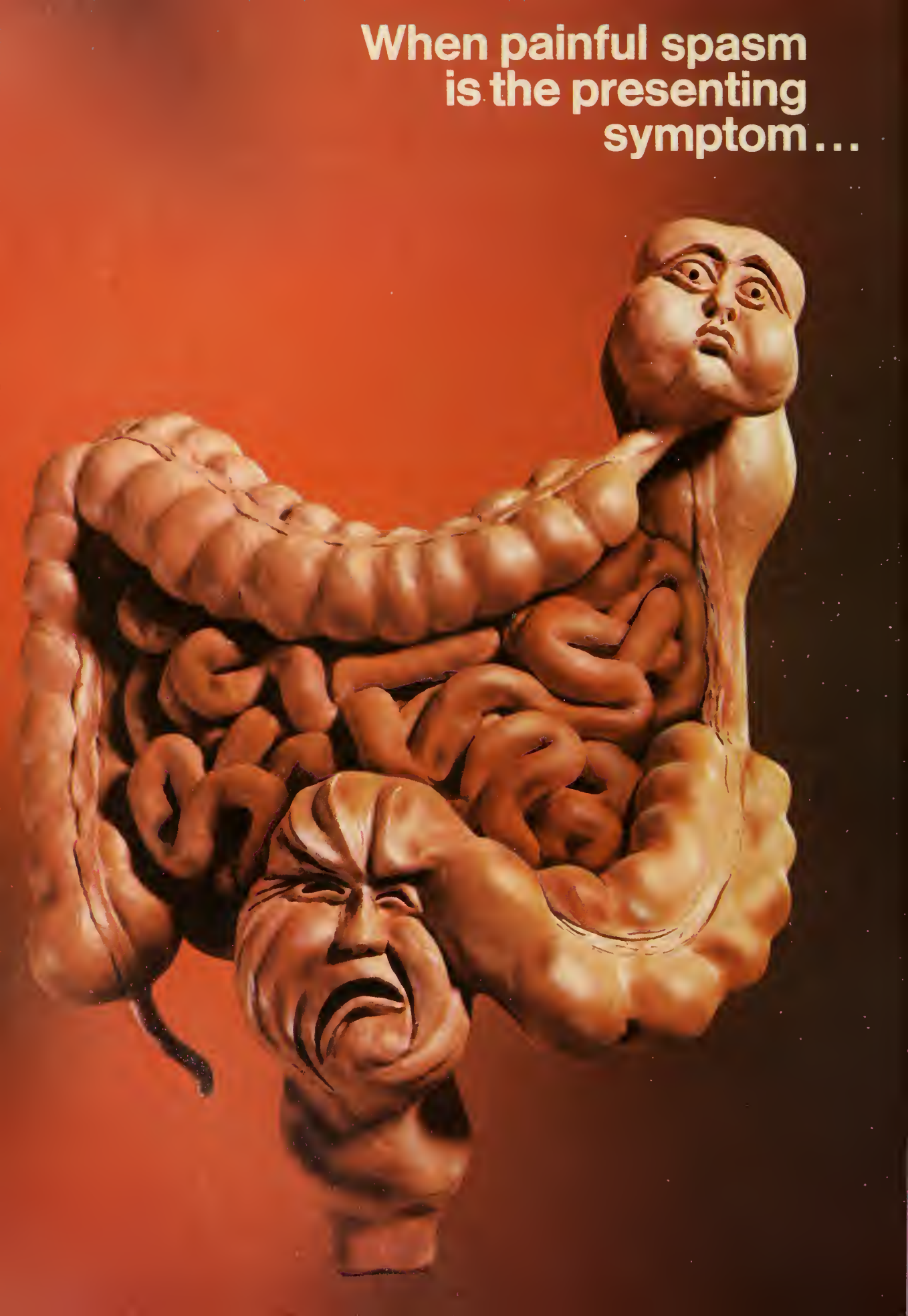
(ISOXSUPRINE HCl)

20-mg tablets

Mead Johnson PHARMACEUTICAL DIVISION

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When painful spasm is the presenting symptom...



...in the functional bowel/irritable bowel syndrome*

Bentyl®

(dicyclomine hydrochloride USP)

10 mg. capsules, 20 mg. tablets,
10 mg./5 ml. syrup, 10 mg./ml. injection

helps control abnormal motor activity
with minimal anticholinergic side effects†

Demonstrated smooth muscle relaxant activity.

In this double-blind study, twenty patients having G.I. series and exhibiting spasm were randomly selected to receive either 2 cc. of Bentyl or sodium chloride intramuscularly. Ten minutes after the injection another radiograph was taken . . .

. . . Bentyl produced definite relaxation in 8 of 10 patients. The sodium chloride produced relaxation in only 3 of 10. No side effects occurred in either group of patients.



Pylorospasm has almost totally blocked passage of barium meal.



Barium meal beginning to pass 10 minutes after intramuscular injection of 20 mg. Bentyl.

"The correlation of spasm relief and drug given was excellent."

*This drug has been classified "probably" effective in treating functional bowel/irritable bowel syndrome

†See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964

Merrell

8-4420 (Y736A) MNR-804

Bentyl®

(dicyclomine hydrochloride USP)

Capsules, Tablets, Syrup, Injection

AVAILABLE ONLY ON PRESCRIPTION

Brief Summary

INDICATIONS

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the following indications as "probably" effective.

For the treatment of functional bowel/irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

THESE FUNCTIONAL DISORDERS ARE OFTEN RELIEVED BY VARYING COMBINATIONS OF SEDATIVE, REASSURANCE, PHYSICIAN INTEREST, AMELIORATION OF ENVIRONMENTAL FACTORS.

For use in the treatment of infant colic (syrup).

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis; toxic megacofon complicating ulcerative colitis; myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or cofostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: Autonomic neuropathy. Hepatic or renal disease. Ulcerative colitis: Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension. Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include: xerostomia; urinary hesitancy and retention; blurred vision and tachycardia; palpitations; mydriasis; cycloplegia; increased ocular tension; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally focal irritation. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs.

Usual Dosage: Bentyl 10 mg. capsule and syrup: *Adults*: 1 or 2 capsules or teaspoonfuls syrup three or four times daily. *Children*: 1 capsule or teaspoonful syrup three or four times daily. *Infants*: ½ teaspoonful syrup three or four times daily. (May be diluted with equal volume of water.) Bentyl 20 mg. *Adults*: 1 tablet three or four times daily. Bentyl Injection: *Adults*: 2 ml. (20 mg.) every four to six hours intramuscularly only. NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE: The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

Product Information as of October, 1978.

Injectable dosage forms manufactured by CONNAUGHT LABORATORIES, INC., Swiftwater, Pennsylvania 18370 or TAYLOR PHARMACAL COMPANY, Decatur, Illinois 62525 for MERRELL-NATIONAL LABORATORIES, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215, U.S.A.

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Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215 U.S.A.

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Body Image in CVA Patients

ANNA B. ORBETON, OTR* AND MARGARET MALESKI, COTA*

During the one-year period between December of 1976 and 1977, twenty-one patients with the diagnosis of CVA with right hemiparesis, thirty-three patients with the diagnosis of CVA with left hemiparesis, and five patients of undefined CVA's were admitted to National Medical Care of Portland, Inc. All of the patients who receive an occupational therapy order from a physician are functionally evaluated, perceptually evaluated (when indicated), and treated accordingly.

As part of the perceptual evaluation, patients are usually asked to draw a full figure as an indication of body image impairment. The drawing goes in the patient's chart with the evaluation. Randomly, some of these drawings were Xeroxed without the patient's name as a teaching aid for students who have spent varying periods of time in our Occupational Therapy Department.

This article is confined to the seven patients whose full figure drawings could be identified and whose records were readily available. Of the seven patients, five females and one male were diagnosed as CVA's with left hemiparesis, and one male was diagnosed a CVA with right hemiparesis and expressive-receptive aphasia. One female left hemiparesis patient was left-handed. The other patients were all right-handed. The average age of these patients was 72½ years. The total number of days at National Medical Care of Portland, Inc. was 842. They received 242 occupational therapy treatment sessions for re-education of the affected upper extremity, hemiplegic techniques in self-care, and perceptual training.



Fig. 1



Fig. 2





Fig. 3 **Fig. 4**

By listing self-care feeding, bathing of the upper and lower extremities, and dressing of the upper and lower extremities, there are a total of 35 areas for grading of, "unable to assist," "able to assist," and "independent once set-up." On admission, there were 17 unable to assist, 12 able to assist, and 6 independent once set-up. The totals at discharge, in-

*National Medical Care of Portland, Inc., 13 Charles Street, Portland, Maine 04102.

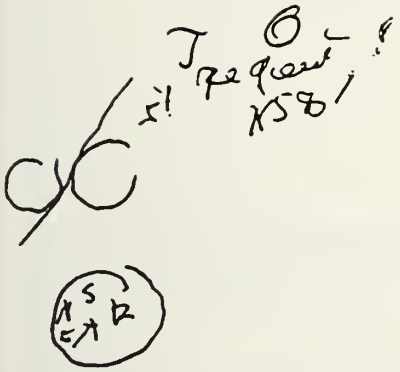


Fig. 5



Fig. 6

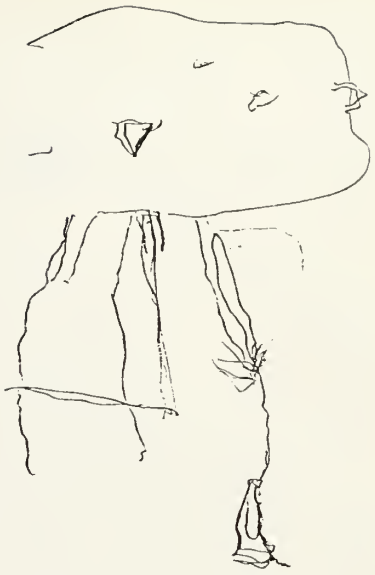


Fig. 7

cluding the patient who died unexpectedly, were 7 unable to assist, 13 able to assist, and 15 independent once set-up.

All seven patients had a tendency, in varying degrees, to neglect the affected side in their self-care activities. Perception is not how one sees, but how one interprets what one sees and feels. Examples of this body image impairment are illustrated in the seven drawings by these patients. Good functional return is not an indication that the arm will be used when there is little or no awareness of the limb.

Of the six patients for discharge three females and one male went to nursing homes, one patient went home under the care of her husband and family, and one patient went home under the care of his wife. The last patient, I might add, took advantage of his wife's sleeping late one morning by driving his car in to see us. He may have compensated well for his left neglect but continued to show the lack of judgment common in CVA patients with left hemiparesis.

Reminder to M.M.A. Members

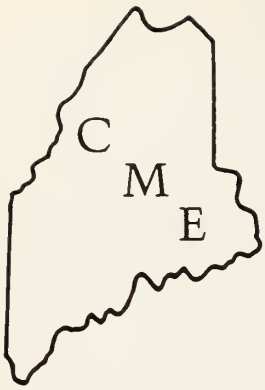
CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The Maine Medical Association's House of Delegates, at its June 1976 meeting, adopted a regulation stating that a *minimum of 150* hours of continuing medical education is required in order to maintain membership. The policy took effect on January 1, 1977 and all members must be certified by January 1, 1980. Eligibility for certification begins January 1, 1977.

Credits required for the three-year period are as follows:

Category 1 — CME Activities with Accredited Sponsorship **(60 hours required)**	**No limit**
Category 2 — CME Activities with Non-accredited Sponsorship	**45 hours**
Category 3 — Medical Teaching	**45 hours**
Category 4 — Papers, Publications, Book and Exhibits	**40 hours**
Category 5 — Non-supervised individual CME Activities	**45 hours**
Category 6 — Other Meritorious Learning Experience	**45 hours**

Only active, dues-paying members are required to report. Please fill in your activity report promptly and return to the M.M.A. office, P. O. Box 250, Brunswick, Maine 04011.



CONTINUING MEDICAL EDUCATION IN MAINE

Conferences and Workshops

Title: **A Day of Learning at Skowhegan**
Sessions on: Neurology, Gastroenterology, Infectious Disease, Endocrinology, and Cardiology
Date: June 6, 1979; 8:30 A.M.-5:30 P.M.
Location: Redington-Fairview Hospital; Skowhegan
Sponsors: Medical Education Consortium and Medical Care Development, Inc.
Credit: AMA Category I—7½ hours; AAFP (being applied for)
Reg. Fee: None
If you do plan to attend please notify David Ginder, M.D.; 873-0621, prior to June 1, 1979.

Title: **Fifth Annual Maine Biomedical Science Symposium**
Sessions on: Alcoholism, Behavior and Life Span Development, Nutrition and Cancer, Human Genetics, Developmental Biology, Cell and Molecular Biology, Introductory College Science Teaching
Date: June 14-15, 1979
Location: University of Maine at Orono (UMO)
Sponsors: UMO and The Jackson Laboratory, Bar Harbor
Reg. Fee: $15.00
For further information contact John M. Ringo; 581-7695.

Title: **Maine Medical Association's Annual Scientific Session**
Date: June 18 and 19, 1979; 9:00 A.M.
Location: Samoset Resort Inn; Rockport
Sponsors: Maine Medical Association and Medical Care Development, Inc.
Credit: AMA Category I—10 hours
Reg. Fee: None
For further information contact Patricia A. Bergeron; 725-6414

Title: **Sports Medicine Seminar**
Date: June 27-30, 1979
Location: Bowdoin College, Brunswick
Sponsors: Bowdoin College; Regional Memorial Hospital; Medical Care Development, Inc.
Credit: AMA Category I—19 hours
Reg. Fee: $220.00
For further information contact Joanne C. LeBlanc, 729-0181.

Title: **Management Systems for Hospital Cost Containment**
Date: August 16-18, 1979
Location: Shawmut Inn; Kennebunkport
Sponsor: Maine Hospital Association; Maine Voluntary Cost Containment Committee
For further information contact Margery Read; 622-4794

Title: **Family Medicine—Update**
Date: September 24-26, 1979
Location: Samoset Resort Inn, Rockport
Sponsor: Medical Care Development, Inc.
Credit: AMA Category I—15 hours; AAFP (prescribed)—15 hours
Reg. Fee: $150.00
For further information contact Gerald Goold; 622-7566

Programs Sponsored by Mid-Maine Medical Center/Colby College

Title: **Allergy and Immunology**
Date: July 2-5, 1979
Location: Colby College
Credit: AMA Category I—16 hours; AAFP (elective)—16 hours
Reg. Fee: $250.00

Title: **Topics in Emergency Medicine**
Date: July 8-12, 1979
Location: Dean Auditorium, Mid-Maine Medical Center (MMMC)
Credit: AMA Category I—22 hours; AAFP (prescribed)—22 hours
Reg. Fee: $275.00

Title: **Epilepsy Seminar**
Date: July 10-14, 1979
Location: Colby College
Credit: AMA Category I—19 hours; AAFP (elective)—19 hours
Reg. Fee: $235.00

Title: **Topics in Pediatrics**
Date: July 15-19, 1979
Location: Colby College
Credit: AMA Category I—17 hours; AAFP (elective)—17 hours
Reg. Fee: $210.00

Title: **Surgical Techniques and Problems**
Date: July 17-20, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—15 hours
Reg. Fee: $185.00

Title: **Hematology—Disorders of Maturation and Proliferation**
Date: July 22-26, 1979
Location: Colby College
Credit: AMA Category I—18 hours
Reg. Fee: $225.00

Title: **Neurosurgical Techniques**
Date: July 22-26, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—21 hours
Reg. Fee: $260.00

Title: **Office Dermatology**
Date: July 29-August 2, 1979
Location: Colby College
Credit: AMA Category I—16 hours; AAFP (elective)—16 hours
Reg. Fee: $200.00

Title: **F.T. Hill Seminar in Otolarngology**
Date: July 29-August 2, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—18 hours
Reg. Fee: $225.00

Title: **Ophthalmology Seminar**
Date: August 5-9, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—18 hours
Reg. Fee: $225.00

Title: **Topics in Clinical Nuclear Medicine**
Date: August 12-17, 1979
Location: Colby College
Credit: AMA Category I—30 hours
Reg. Fee: $350.00

Title: **Current Aspects of Obstetrics and Gynecology**
Date: August 12-16, 1979
Location: Colby College
Credit: AMA Category I—18 hours
Reg. Fee: $225.00

Title: **Continuing Topics in Forensic Sciences**
Date: August 19-23, 1979
Location: Colby College
Credit: AMA Category I—21 hours
Reg. Fee: $275.00

Title: **Topics in Pulmonary Disease**
Date: August 19-23, 1979
Location: Colby College
Credit: AMA Category I—19 hours
Reg. Fee: $240.00

For further information on all the programs sponsored by Mid-Maine Medical Center/Colby College, contact Robert H. Kany, Ph.D.; Division of Special Programs, Colby College; Waterville, Maine 04901; 873-1131

Hospital Activities

Augusta General Hospital
Augusta, Maine

June 26, 1979 — **Dermatology Conference**
7:30-8:30 a.m. — Daniel Clarke, M.D., Augusta General Hospital

July 24, 1979 — **Endocrine Conference**
7:30-8:30 a.m. — Hugh Johnston, M.D., Thomas Bigos, M.D., or Richard Eastman, M.D., Maine Medical Center

Programs have been certified AMA Category I and AAFP (prescribed). For further information contact Mrs. Nancy York; 623-4711. Programs may be viewed over ITS.

Dean Hospital
Greenville, Maine

June 15, 1979 — **Clinical Consultations—Urology**
9:30 a.m.-Noon — Earle Davis, M.D., MMMC

July 20, 1979 — **Clinical Consultations—Cardiovascular Disease**
9:30 a.m.-Noon — Larry Nolin, M.D., MMMC

Programs have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621.

Eastern Maine Medical Center
Bangor, Maine

Every Mon.	EEG Conference	12-1 p.m.
Every Mon.	Surgical Service—Chief's Rounds	5-6 p.m.
3rd Tues.	Dermatology-Pathology Conference	5-6 p.m.
3rd Tues.	Dermatology Section Meeting	6-7 p.m.
4th Tues.	Pulmonary Medicine Section Meeting	8-9 a.m.
1st Wed.	Hematology/Oncology Meeting	8-9 a.m.
Every Wed.	Tumor Clinic Conference	2-5 p.m.
Every Wed.	Radiology Conference (1) Ultrasound/Nuclear Medicine (2) Radiology Film Review (3) Neuroradiology (4) Teaching File Conference	5-6 p.m.
1st Thurs.	Ophthalmology Section Meeting	7:30-8:30 a.m.
	OB-GYN Conference (1) Pathology (2) GYN Analysis (3) OB-Pediatric Combined (4) In-Service and Education	8-9 a.m.
Every Thurs.	Pediatric Grand Rounds	9-10 a.m.
Every Thurs.	Medical Service Conference	10-11 a.m.
Every Thurs.	Cardiology Conference	11 a.m.-1 p.m.
2nd Thurs.	Orthopedic Grand Rounds	7:45-8:45 a.m.
4th Thurs.	Orthopedic Service Meeting	7:30-9 a.m.
4th Thurs.	Surgical Service Death Review	7:45-8:45 a.m.
Every Thurs.	Psychiatric Service Grand Rounds	10-11 a.m.
4th Thurs.	Urology Section Conference	7:30-8:30 a.m.
Every Fri.	Neurology Grand Rounds	8-9 a.m.

Visiting Professor Program:

2nd Thurs.	Medical Service Visiting Professor	10 a.m.-5 p.m.
2nd Thurs.	Anesthesia Service Visiting Professor	7-8 a.m.
3rd Thurs.	OB/GYN Service Visiting Professor	10 a.m.-4 p.m.
Saturdays	Surgery Service Visiting Professor	8 a.m.-Noon
4th Thurs.	Pediatric Service Visiting Professor	10 a.m.-5 p.m.
as scheduled	Orthopedic Service Visiting Professor	
as scheduled	Family Practice Visiting Professor	
as scheduled	Psychiatric Service Visiting Professor	

All activities have been certified AMA Category I. For information contact Robert H. Brown, M.D., Chairman, Med. Ed. Committee; 947-3711 Ext. 330.

Franklin County Hospital
Farmington, Maine

July 2, 1979 — **Immunology-Allergy Conference**
6-8:30 p.m. — Robert Sylvester, M.D., CMMC, and Geoffrey Gratwick, M.D., EMMC

All activities have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621

Henrietta D. Goodall Hospital
Sanford, Maine

June 21, 1979 — **What the Physician Should Know About Occupational Disease**
Larry Fine, M.D., Harvard School of Public Health

The meetings will be held at the Henrietta D. Goodall Hospital's Conference Room at 7 p.m. For further information contact Melvin Bacon, M.D., 324-3632.

A. R. Gould Memorial Hospital
Presque Isle, Maine

May 28, 1979: — No Meeting—Memorial Day

June 4, 1979 — **Colonization and Suprainfection**
Richard Brown, M.D., Bay State Medical Center, Springfield, Mass.

June 11, 1979 — **Antibiotic Therapy of Intra-Abdominal Infections**
Philip B. Mead, M.D., Un. of Vt. College of Medicine

Weekly Grand Rounds are held in the Rotary Room beginning at 7:30 p.m.; programs have been certified AMA Category I. For further information contact David Skinner, M.D., 769-2511.

Maine Medical Center
Portland, Maine

Every Tues. 9-10:30 a.m. **Arthritis Rounds** (speakers to be determined)

For further information contact Albert Aranson, M.D.; 871-1011.

Mid-Maine Medical Center
Waterville, Maine

May 31, 1979 **Cancer Chemotherapy**
Larry Nathanson, M.D., Tufts University School of Medicine

June 14, 1979 **Electrolyte Theories**
Jerome Kassirer, M.D., Tufts University School of Medicine

June 28, 1979 **Obstetrics**
David Nochimson, M.D., Bay State Medical Center, Springfield, Mass.

All programs run from 12-1 p.m. and have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D., 873-0621. Programs may be viewed over ITS.

Plummer Memorial Hospital
Dexter, Maine

June 6, 1979 1 - 4 p.m. **Clinical Consultation—Pediatrics**
Eugene Peters, M.D., MMMC

All activities have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621.

Redington Fairview Hospital
Skowhegan, Maine

May 30, 1979 10:30 a.m.-2 p.m. **Visiting Professor—Pediatrics**
Murray Feingold, M.D., Tufts University School of Medicine

June 27, 1979 12-1 p.m. **Endocrinology Conference**
Richard Eastman, M.D., Maine Medical Center

All activities have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621.

Sebasticook Valley Hospital
Pittsfield, Maine

June 6, 1979 9 a.m.-Noon **Office Gynecology**
Donald Coulton, M.D., EMMC

All activities have been certified AMA Category I. For further information contact David Ginder, M.D.; 873-0621

V. A. Hospital
Togus, Maine

June 4, 1979 **Staff Meeting—Research Service**

June 6, 1979 **Medical Service Staff Meeting—Case Presentation**

June 12, 1979 **Staff Meeting—Laboratory Service** (On ITS)

June 13, 1979 **Medical Service Staff Meeting—Review of Records**

June 15, 1979 **Neuro-Behavioral Aspects of Dementia**
Frank Benson, M.D., Associate Chief of Staff, Boston V.A. Medical Center

June 20, 1979 **Medical Service Staff Meeting—Case Presentation**

Programs have been certified AMA Category I. For further information contact E. Osborne Coates, Jr., M.D.; 623-8411.

Special ITS Programs

Title: **Medically Intractable Epilepsy**
Sessions: **Approaches and Resources for Management**
R.J. Porter, M.D., Assistant Chief, Epilepsy Branch, National Institutes of Health
Surgical Treatment
P.H. Crandall, M.D., Professor of Surgery, UCLA School of Medicine
Date: May 23, 1979; 7-9 p.m.
Location: May be viewed from all ITS locations (MMMC, CMMC, AGH, VA, and SMGH). (live via satellite)
Sponsor: Medical University of South Carolina
Credit: AMA Category I—$5.00 per program
AAFP Credit—$5.00 per program
Reg. Fee: None
For further information contact Robert A. Cowan; 622-7566

Title: **Consequences of Epilepsy**
Sessions: **Behavioral Problems**
L.J. Willmore, M.D., Assistant Professor of Neurology, University of Florida and VA Hospital
The Human Experiences
R.L. Masland, M.D., Emeritus Professor of Neurology, Columbia University
Prospects for the Future
R.L. Masland, M.D., Emeritus Professor of Neurology, Columbia University
Date: May 30, 1979; 7-9 p.m.
Location: May be viewed from all ITS locations (MMMC, CMMC, AGH, VA, and SMGH). (live via satellite)
Sponsor: Medical University of South Carolina
Credit: AMA Category I—$5.00 per program
AAFP Credit—$5.00 per program
Reg. Fee: None
For further information contact Robert A. Cowan; 622-7566

From the Secretary's Notebook

Summary of 1978 Fall Meeting of the M.M.A. House of Delegates

December 9, 1978 at Waterville, Maine

The Fall Meeting of the M.M.A. House of Delegates was held at the Mid-Maine Medical Center (Thayer Unit) in Waterville on Saturday, December 9, 1978, with an attendance of 56 Delegates and Alternates, and six guests. Francis I. Kittredge, M.D., President of the M.M.A. called the meeting to order and George W. Bostwick, M.D., Speaker of the House, presided.

1. Reports of Officers:

a) Dr. Kittredge, President, reported on the consent decree issued in the *10% cut suit.*

Dr. Kittredge urged the members to become more involved in *legislative issues*, and know their legislators preferably in advance of the legislative session.

b) Dr. McAfee, Delegate to the *American Medical Association*, gave a report on the recent convention in Chicago. Major issues discussed were physician advertising, chiropractic and national health insurance.

2. Committee Reports:

a) *Negotiations*—Dr. Richard Leck, Chairman, explained the charge of the committee, and made specific recommendations.

b) *Building Committee*—Dr. John Wickenden, Chairman, introduced the architects, William Sepe and Steve Smith, who presented a slide and lecture review of their preliminary plans for the M.M.A. headquarters to be located in Augusta. A *preliminary budget* was presented by Mr. Sepe as follows:

1. Building: 3404 sq. ft. @ $40.00/sq. ft.		$136,160.00
2. Solarium, including floor		10,000.00
3. Excavation and Landscape, incl. courtyard & parking		15,000.00
Moving Trees	$ 500.00	
New Trees	700.00	
55 cu. yds. loam & seed	1,500.00	
Bitum.	5,000.00	
Excavation 2222 cu.yds.	3,500.00	
Courtyard, drains, etc.	3,800.00	
4. Furnishings:		7,500.00
5. Architectural and Engineering Fees (9% maximum)		18,000.00
Project Cost		186,660.00
@ $45.00/sq.ft.	add.	+ 20,000.00
		$206,660.00

Many questions were answered re insulation, heat source, plumbing, cost per foot, rental options in Augusta, etc. Concern was expressed re how this was going to be paid for. Dr. Feagin spoke for the *Building Finance Committee*, and said "his committee will be meeting and will report at the next meeting of the House of Delegates on suggested methods for financing. The delegates were reminded also that a $100 building assessment was previously approved by the House of Delegates, and could be collected if need be."

The architect assured the delegates that between this meeting and the next, bids will be obtained with a choice of options and price ranges for the delegates to review. No final contract for building will be signed without the approval of the House of Delegates. A packet of information, prepared by Mr. Sepe, was distributed to the delegates. It included a sketch of the site and floor plans, and information on site location, site analysis, building program and low energy building concept.

Mr. Sepe said he will be sending out the plans for cost analysis in the next two weeks. The next estimate will be more detailed, and will come within 10-15% of actual costs, Mr. Sepe added.

A motion that the Building Committee proceed with the present plans, and return with definite specifications and options for financing (from the Building Finance Committee) at the Spring Meeting of the House of Delegates and this was *approved.*

3. Resolutions—Three resolutions were presented to the delegates (copies sent to all delegates on 12/4/78), and all will be referred to the June 1979 meeting of the House of Delegates for action.

4. Relationship with **Blue Shield**—Dr. Peter Shrier reported on several sessions that have been held over the past six months and sees the following options available: a) terminate the existing Blue Shield contract; b) continue with the present program; c) settle for what has been achieved so far; or d) end all negotiations. Following considerable discussion, a motion was made that the House of Delegates instruct the Committee on Health Care Financing to negotiate with Blue Shield from the position that we want equal benefits for the patients of non-participating physicians. This was *approved* in a light vote.

Continued on Page 213

COST CONTAINMENT INCENTIVE PROGRAM

The Board of Directors of Blue Cross and Blue Shield of Maine has placed a high priority on cost containment efforts and in support of this objective, has established a Cost Containment Incentive Program.

The purpose of the program is to solicit cost containment ideas and projects from all segments of the health care community—subscribers, professionals, hospitals, group purchasers, the general public, etc. The Committee will solicit cost containment ideas and projects with a view toward promoting ideas that hold promise and providing some measure of financial support to those projects which are approved by the Board of Directors, which have cost containment potential.

Cost containment ideas and projects must meet at least one of the following criteria in order to be considered for an award or financial support:

1. The proposal must have a clear potential for increasing productivity within the health care system without an equal or greater increase in operating costs.
2. The proposal must have a clear potential for reducing the rate of escalation of operating costs.
3. The proposal must have a clear potential for controlling or reducing the rate at which health care services are requested/used.
4. There must be an opportunity for practical application of the idea or project.

In the case of projects found acceptable by the Cost Containment Incentive Program Committee, one of several types of support may be offered by Blue Cross and Blue Shield of Maine. These include:

1. Providing seed money for the project.
2. Providing a grant for implementation of the project.
3. Providing an interest free loan to support the project.
4. Arranging for the project sponsors to share in the demonstrated savings to Blue Cross and Blue Shield.

Cost containment ideas determined by the Cost Containment Incentive Program Committee to meet the necessary criteria will be awarded monetary prizes. Acceptable ideas will be published to the health care community with appropriate credit given to the author.

There no longer is a question of whether the industry should attempt to reduce the rate of increase in costs, but rather how it should do so. Cost effectiveness requires the wholehearted and active support of all segments of the health care industry, the professionals, institutions, suppliers, payors, the consumer public and government. If the industry is to meet the challenge it must enlist the participation and cooperation of all of these elements.

Please forward your recommendations or inquiries to:

Daniel G. Willett
Cost Containment Committee
Blue Cross and Blue Shield of Maine
110 Free Street
Portland, Maine 04101

Necrologies

Harold W. Stevens, M.D.
1883-1978

Dr. Harold W. Stevens, 95, of Saco, Maine, died on October 1, 1978 in a Biddeford nursing home following a lengthy illness.

Born in Saco, Maine on June 16, 1883, he was the son of Charles and Frances R. Stevens.

He was graduated from Bates College and received his medical degree from Harvard Medical School in 1914. Dr. Stevens interned at the Massachusetts General Hospital and took postgraduate courses at the Harvard School of Public Health.

Dr. Stevens was engaged in the practice of occupational medicine with Ludlow Manufacturing Associates in Ludlow, Massachusetts and Jordan Marsh Company in Boston, Massachusetts from 1920-1930, was local Health Officer and State District Health Officer in Massachusetts from 1931 to 1953, and was on the staff at Tobey Hospital in Wareham, Massachusetts from 1945 to 1953. He returned to Saco in 1953 and was Physician Advisor for York County Head Start, York County Child and Family Guidance, York County Council on Aging and State Advisory Committee on Aging.

During World War I, he served in the Royal Army Medical Corps and the U.S. Army Medical Corps as a Major.

An honorary member of the York County Medical Society and the Maine Medical Association, he received a 50-year pin in 1965, a 55-year pin in 1970 and a 60-year pin in 1975. He was also a member of the American Medical Association, the Massachusetts Medical Society, the American Public Health Association, the Massachusetts Department of Public Health and the American College of Physicians.

Surviving are a son, Prescott A. of Geneva, Switzerland; two daughters, Mrs. Joan F. Gross of Saco and Mrs. Anne P. Mitchell of Portland, Oregon; and nine grandchildren.

Paul E. Taylor, M.D.
1914-1978

Dr. Paul E. Taylor, 64, of Kittery, Maine, died at a Boston hospital on November 6, 1978.

Born in Saugus, Massachusetts on October 15, 1914, he was the son of Oscar E. and Dorcas P. Taylor.

He was graduated from the University of Maine, received his medical degree from Tufts University School of Medicine in 1940 and interned at the Maine General Hospital. He had practiced in Kittery since 1941.

Dr. Taylor was a member of the York County Medical Society, the Maine Medical Association, the Portsmouth Medical Society and the Rockingham Medical Society. He was also a member of the Portsmouth Hospital staff since 1951 and the courtesy and consultant staff of the York Hospital.

Surviving are a brother, Robert Taylor of Denver, Colorado; and two sisters, Mrs. Elizabeth Gay and Mrs. Ruth Vocca, both of Kittery.

John J. Busch, M.D.
1901-1978

Dr. John J. Busch, 77, of Mechanic Falls, Maine, died unexpectedly at the Central Maine Medical Center on November 7, 1978.

He was born in Medway, Massachusetts on August 16, 1901, the son of John J. and Lucy M. Busch.

Dr. Busch was graduated from Bates College and received his medical degree from the University of Vermont College of Medicine in 1929. He interned at the Central Maine General Hospital. In 1930, he located in Mechanic Falls.

He was a senior member of the Androscogin County Medical Society, the Maine Medical Association and the American Medical Association.

Surviving are his widow, Elizabeth C. Busch of Mechanic Falls; two daughters, Mrs. Robert Begley of Houston, Texas and Mrs. Gerald Fuller, of Waterville; a son, Harry J. of Poland; and eight grandchildren and one great-grandchild.

Albert W. Moulton, Sr., M.D.
1887-1978

Dr. Albert W. Moulton, Sr., 91, of Portland, Maine, died on December 5, 1978 following a long illness.

He was born in South Portland, Maine on June 26, 1887, the son of Willis B. and Estelle M. Moulton.

Dr. Moulton was graduated from Bowdoin College and received his medical degree from Bowdoin Medical School in 1913. He interned at the Maine General Hospital and took a postgraduate course at the Manhattan Eye, Ear and Throat Hospital.

He had practiced in the Portland area since 1913 and was affiliated with the Maine General Hospital, the Maine Eye and Ear Infirmary, the Maine Medical Center, the Mercy Hospital and the Webber Hospital. Dr. Moulton was a consultant of the ophthalmology department of the Maine General Hospital from 1949-1953, chief of staff of the Maine Eye and Ear Infirmary from 1923-1953 and an honorary staff member of the Mercy Hospital.

Dr. Moulton was appointed U.S. Public Health Surgeon from 1912 until 1924, and was Emergency Medical Director for the State of Maine from 1942 until 1944. He was civil protection advisor in the Medical Division for the Office of Emergency Management. In 1950, he was appointed Deputy Director in charge of medical aspects of Civil Defense and Public Safety for the State of Maine.

An honorary member of the Cumberland County Medical Society and the Maine Medical Association, he received a 50-year pin in 1963, a 55-year pin in 1968, a 60-year pin in 1973 and a 65-year pin in 1978. He was also a member of the American Medical Association.

Surviving are a son, Dr. Albert W., Jr., of Scarborough; a sister, Mrs. Arch H. Morrell of South Portland; six grandchildren and five great-grandchildren.

John A. Woodcock, M.D.
1922-1978

Dr. John A. Woodcock, 55, of Bangor, Maine, died on December 21, 1978 at a Portland hospital after a short illness.

Born in Bangor, Maine on December 27, 1922, he was the son of Dr. Allan and Priscilla Woodcock.

He was graduated from Bowdoin College, received his medical degree from Cornell University Medical School in 1946, interned at New York Hospital, and served a residency at Eastern Maine General Hospital before serving a resident junior fellowship at New York Orthopedic Hospital from 1948 to 1951. He established his practice in Bangor in 1951. From 1954 to 1956, he served in the Medical Corps of the U.S. Navy as a Lieutenant Commander.

Dr. Woodcock was a member and past president of the Penobscot County Medical Society, a member of the Maine Medical Association, the American Medical Association, the American Academy of Orthopedic Surgeons, the New England Surgical Society, a diplomat of the American Board of Orthopedic Surgery and a fellow of the American College of Surgeons. He was also chief of staff of orthopedic services at Eastern Maine Medical Center, 1956-1978, president of staff at Eastern Maine Medical Center, 1975-1977, a member of the staff at St. Joseph Hospital and was consultant for numerous Maine hospitals.

Surviving are his widow, Joan Woodcock; seven children, Mrs. William D. Keitzman of Plymouth, New Hampshire, Mrs. John M. Templeton of Marlo Park, California, Mrs. Robert Ervin of Machias, John A. Woodcock, Jr. of Orrington, Timothy C. Woodcock of Bangor, Elizabeth C. Woodcock of Bangor and G. Andrew C. Woodcock of Bangor; one brother, Allan Woodcock, Jr. of Bangor; one sister, Mrs. Jothan D. Pierce of Portland; and three grandchildren.

Robert M. McQuoid, M.D.
1903-1979

Dr. Robert M. McQuoid, 75, of Brewer, Maine, died on January 1 at a Bangor hospital following a brief illness.

He was born in Coulterville, Illinois on November 10, 1903, the son of the Rev. Thomas N. and Nettie P. McQuoid.

Dr. McQuoid was graduated from Muskingum College, New Concord, Ohio and received his medical degree from Case Western Reserve University School of Medicine in 1930. He served his internship and residency at Lakeside Hospital in Cleveland. In 1934, he located in Bangor where he was on the staff of the Eastern Maine Medical Center since 1935 and served as President in 1955. He was also on the staff of St. Joseph Hospital.

A senior member of the Penobscot County Medical Society and the Maine Medical Association, he was also a member of the American Medical Association, the American Board of Otolaryngology, the New England Otolaryngology Society and the American Academy of Ophthalmology and Otolaryngology.

Surviving are his widow, Esther M. McQuoid of Holden; a daughter, Jean M. Duhaime of Holden; three sons, Thomas N. of New York, Robert N. of Holden and William G. of Connecticut; and six grandchildren.

Mason Trowbridge, Jr., M.D.
1910-1979

Dr. Mason Trowbridge, Jr., 68, of Brewer, Maine, died on February 4 at the Eastern Maine Medical Center in Bangor.

Born in Port Washington, New York on April 5, 1910, he was the son of Mason and Helen F. Trowbridge.

He was graduated from Yale University and received his medical degree from Columbia University College of Physicians and Surgeons in 1937. He interned at the Bellevue Hospital in New York.

Dr. Trowbridge started his practice in Ellsworth in 1941. From 1942 to 1946, he served in the U.S. Air Force as a Major. In 1957, he moved to Bangor where he practiced until retiring in 1978. He subsequently continued his research on pernicious anemia.

An affiliate member of the Penobscot County Medical Society and the Maine Medical Association, he was also a member of the American Medical Association and past president of the Maine Chapter, American Society of Internal Medicine.

Surviving are his widow, Elizabeth C. Trowbridge of Brewer; three daughters, Helen Trowbridge of New York City, Mrs. Robert Wild of Fairport, New York and Jane T. Bertrand of New Orleans, Louisiana; one sister, Harriet G. Trowbridge of West Cornwall, Connecticut; two brothers, George F. Trowbridge of McLean, Virginia and James R. Trowbridge of Westfield, New Jersey; and three grandchildren.

George J. Robertson, M.D.
1915-1979

Dr. George J. Robertson, 63, of Belgrade Lakes, Maine, New England medical educator and Associate Dean for Medical Education of the Tufts University School of Medicine Program in Maine, died on February 22 at the Mid-Maine Medical Center in Waterville after a long illness.

He was born on September 29, 1915 in Lawrence, Massachusetts, the son of Albert and Mary M. Robertson.

Dr. Robertson was graduated from Tufts College and received his medical degree from Tufts University School of Medicine in 1943. He interned at the Boston City Hospital and served residencies at the Pratt Diagnostic Hospital and the Boston City Hospital.

He set up a private practice in Waterville and became that city's first board-certified physician of internal medicine. During 15 years of practice in Waterville, he served as medical director of Sisters Hospital, Chief of Medicine and Director of medical education at Thayer Hospital, now known as the Mid-Maine Medical Center. In 1963, Dr. Robertson returned to Boston to become Medical Director of the Bingham Program, a medical project based at New England Medical Center Hospital, for continuing education of physicians in rural areas, particularly in Maine, and served as senior physician at the New England Medical Center Hospital and Assistant Professor of Medicine at Tufts. In September of 1977, he returned to Maine to help establish the first year-round medical clinic in the Belgrade Lakes region.

In 1962, he received the A.H. Robins' Physicians Award for outstanding community service at the Maine Medical Association's annual session.

Dr. Robertson was an affiliate member of the Kennebec County Medical Association, the Maine Medical Association and the American Medical Association. He also served as Alternate Delegate to the American Medical Association from January 1, 1961 to January 1, 1963, was a former president of the Massachusetts Society of Internal Medicine and a member of the American Board of Internal Medicine.

Surviving are his widow, Lorraine T. Robertson; his father of North Andover, Massachusetts; three sons, James of Derry, New Hampshire, George and Sean, both of Methuen, Massachusetts; four daughters, Myra Meaney of Waterville, Mary Ellen of Hialeah, Florida, Janelle and Anne of Belgrade Lakes; a brother, Albert Robertson of New York City; four sisters, Lillian McDonald, Cathy Lund and Joellen Dittenhaver, all of North Andover, Massachusetts and Eleanor McGuirk of Plaistow, New Hampshire; and three grandchildren.

Harvey C. Bundy, M.D.
1890-1979

Dr. Harvey C. Bundy, 89, of Naples, Maine, husband of Virginia Bundy and widower of Agnes Spencer Bundy, died on February 8 at a local hospital after a long illness.

He was born in Hyde Park, Vermont on January 12, 1890, the son of Harvey H. and Jennie D. Bundy.

Dr. Bundy received his medical degree from the University of Vermont College of Medicine in 1914. He practiced in Brownville Junction from 1914 to 1915, Lake View from 1915 to 1918, Mars Hill from 1921 to 1927, and in Milo from 1927 until his retirement in 1955. He served in the U.S. Army Medical Corps as a 1st Lieutenant during World War I.

He served as Chief Surgeon for the Bangor and Aroostook Railroad for many years, as Chief Surgeon for the Milo Community Hospital from 1928 to 1955, and was Chairman of the Board of Trustees from 1960 to 1969.

An honorary member of the Piscataquis County Medical Society and the Maine Medical Association, he received a 50-year pin in 1964, a 55-year pin in 1969, a 60-year pin in 1974, and would have been eligible to receive a 65-year pin this June.

In addition to his widow, he leaves a daughter, Joyce Wiggin of Providence, Rhode Island; two stepdaughters, Mary Torrey of Newburgh and Sylvia Smith of Bangor; a brother, Stanley Slaton of Malone, New York; a sister, Ola Labare of Morrisville, Vermont; four grandchildren and a great-grandchild.

From the Secretary's Notebook—*Continued from Page 209*

5. Other Business:

a) Dr. McAfee presented four items for information only: 1) the Cumberland County Medical Society is publishing a directory of its membership; 2) the 2nd opinion program is still too new to report any results; 3) the Cumberland County Medical Society gives a $100 Scholarship annually to each high school in its county, and recommends this for other county medical societies as a good public relations project; and 4) the Cumberland County Medical Society is sponsoring a ski vacation to Switzerland this winter and there is room for more couples.

6. Adjourned at 5:05 P.M.

Patricia A. Bergeron
Secretary-Treasurer

County Society Notes—*Continued from Page 220*

2. He also stated that a 10% reduction in fees had been repealed.

3. He also stated that there was a need for a Negotiating Agent to head up a committee to look into negotiations on fees with third party agents.

4. Dr. Kittredge also said doctors should meet with Legislators, particularly new Legislators, that were going to Augusta.

5. Dr. Kittredge also covered the Malpractice set-up and encouraged doctors to join Maine Medical Insurance Company, a mutual company formed by Maine physicians.

This was followed by a discussion about representation on the Executive Committee. It was proposed that Washington County submit a resolution to the House of Delegates that each County have a representative on the Executive Committee. This resolution will be presented by Delegates, Drs. Donald M. Robertson of Harrington and Robert G. MacBride of Lubec.

Dr. Donald M. Robertson spoke on Maternal and Infant Care Plan.

A motion was made, seconded and passed that Washington County Medical Society recognizes the impact on Health Care of the Down East Health Service, and health care in relation to Maternal Infant Care and strongly supports the continuation of MIC Grant the coming and ensuing years.

Dr. Robert G. MacBride stated that the Maine Health Service Agency was setting up Subcommittees. They want five (5) people from Washington County; three (3) would be consumers and two (2) would be providers. He hoped that one provider would be an M.D., and if the physicians had names of any other providers, they should be submitted to HSA.

Dr. Donald M. Robertson of Harrington was elected delegate for 1979 to the Maine Medical Association.

Dr. Robert G. MacBride of Lubec was elected alternate delegate to the Maine Medical Association.

Dr. Toby Acheson of Lubec Medical Center was elected a member of the Washington County Medical Society.

Dr. Richard W. Rowe, Radiologist at the Down East Community Hospital, was elected a member of the Washington County Medical Society.

It was mentioned that the Society had had no visits from a member of the Executive Committee, other than the President, for at least nine (9) years.

The next meeting will be on January 16, 1979.

Karl V. Larson, M.D., *Secretary*

ACOG DISTRICT 1—MAINE & NEW HAMPSHIRE

Combined Section Meeting

Holiday Inn Downtown, 88 Spring Street, Portland, Maine

PROGRAM

WEDNESDAY, JULY 11, 1979

8:00am- 9:15am Registration/Review Displays

9:15am- 9:30am Welcome & Introduction

9:30am-10:15am
Speaker: Alvin F. Goldfarb, M.D., Clinical Professor of Obstetrics and Gynecology, Director of Ambulatory Gynecologic Service, University of Pennsylvania School of Medicine, Pennsylvania Hospital
Topic: "Clinical Problems in Adolescent Gynecology"

10:15am-10:30am Open Forum

10:30am-11:00am Break/Review Displays

11:00am-11:45am
Speaker: George W. Welsh, M.D., Associate Professor of Medicine, University of Vermont College of Medicine, Burlington, Vermont
Topic: "Diabetes Mellitus and Pregnancy"

11:45am-12:00pm Open Forum

12:00pm- 1:00pm Luncheon

1:00pm- 1:45pm
Speaker: Hugh McLaren, M.D., Professor of Obstetrics and Gynaecology, Birmingham University, United Kingdom
Topic: "Thirty Years of Socialized Obstetrics and Gynaecology in Great Britain"

1:45pm- 2:00pm Open Forum

2:00pm- 2:30pm Break/Review Displays

2:30pm- 3:45pm Individual Section Meetings

3:45pm- 4:30pm
Speaker: Eduard G. Friedrich, M.D., Associate Professor, The Medical College of Wisconsin, Milwaukee, Wisconsin
Topic: "Vulvar Pathology"

4:30pm- 5:00pm Open Forum

5:00pm- 8:30pm Clambake & Casco Bay Cruise (with spouses & children)

COGNATES: "This course has been approved for 5 cognates, Formal Learning, by the American College of Obstetricians and Gynecologists."

Registration forms should be mailed by June 15, 1979, as space is limited.

FEE (including luncheon and coffee breaks):
ACOG Fellows...$12.00,* Junior Fellows...$5.00,* Medical Students...no fee

*In the case of Maine and New Hampshire fellows/junior fellows, registration fee is WAIVED, as this has been included in State dues.

Clambake & Cruise*: Adult...$15.00 per person (open bar); Child...$10.00 per person

*Spouses and children are encouraged to attend. Casco Bay is beautiful at this time of the year and the cruise is enjoyed by all!

For additional information, please contact: John Zerner, M.D., FACOG, Chairman, Combination Maine/New Hampshire District Meeting, c/o Gynecological Associates, 260 Western Avenue, South Portland, Maine 04106, Telephone: 207-774-5941.

REGISTRATION FORM

I/We wish to attend the ACOG District 1 Maine/New Hampshire Combined Section Meeting to be held on 11 July 1979 at the Holiday Inn Downtown, Portland, Maine.

Name _____

Address _____
Street City Zip

Fellow _____ Junior Fellow _____ Other _____

Please register me for:

I. Meeting.....Fellow $12.00* _____ Jr. Fellow $5.00* _____ Total _____

II. Clambake @ $15.00 per adult and $10.00 per child _____ Total _____

I would prefer lobster _____ chicken _____.

Total Amount Enclosed $ _____

*Fee Waived for ME/NH fellows/jr. fellows.

Kindly make check payable to ME/NH Combined Section Meeting and mail to:
John Zerner, M.D.
Chairman, ME/NH Combined Meeting
c/o Gynecological Associates
260 Western Avenue
South Portland, Maine 04106

News, Notes and Announcements

Attention Medical History Enthusiasts

If you would like to be a charter member of the Maine Association For Medical History please contact: Richard J. Kahn, M.D., Penobscot Bay Physicians' Building, Rockland, Maine 04841.

Sports Medicine Seminar

Sports Medicine Seminar—a continuing education program on Sports Medicine, June 27-30, 1979. This seminar is designed for physicians and others involved with scholastic and collegiate athletics and/or adults in recreational and exercise programs. Presented by Bowdoin College and Regional Memorial Hospital; cosponsored by Medical Care Development, Inc., meeting criteria for nineteen credit hours in Category I of Physicians Recognition Award of the A.M.A. Enrollment limited to 200.

For further program information contact: Office of Continuing Medical Education, Regional Memorial Hospital, 58 Baribeau Drive, Brunswick, Maine 04011, Area Code 207-729-0181.

Looking for a Physician Assistant or Nurse Practitioner?

Medical Care Development, Inc. maintains an extensive resume file of Physician Assistants and Nurse Practitioners who are interested in employment opportunities in Maine. Anyone considering hiring a physician extender who is interested in obtaining copies of resumes is welcome to contact Peter Grua, Assistant Project Director, Rural Community Health Centers, Medical Care Development, Inc., 295 Water Street, Augusta, Maine 04330, Telephone (207) 622-7566.

Letters to the Editor

To the Editor:

I read Dr. Diggs' paper on Pain, in the Journal of the M.M.A., Vol. 70, No. 2, February 1979, p. 53-59. I could not have read it in its entirety, if it was not for my special interest in pain in general and back pain in particular. Dr. Diggs errs in too many of his pronouncements but I intend to limit myself to few points he makes:

1.) Dr. Diggs' Differential Diagnosis of chronic pain suffers from the omission of not mentioning a most important group of patients; namely, pain as a manifestation of Depressive Equivalents. Pain is known to be one of body's way of crying and as such is treated successfully by psychiatrists every day.

2.) Dr. Diggs admonishes that such patients should not be referred to psychiatrists because they are not "crazy." I think we can all agree that the great majority of these patients are not crazy. On the other hand, the psychogenic nature of these conditions makes a psychiatric consult necessary for any physician mindful of what is good for his patient. Psychological tests or psychologists can not replace the psychiatrist—notwithstanding Dr. Diggs' contention—any more than an EEG can replace a neurologist or an EKG can replace a cardiologist.

3.) Dr. Diggs' "Treatment advice to Physicians" is lacking in many pertinent therapeutic modalities. Pain is treated successfully,

(a.) with antidepressants, electroconvulsive therapy and occasionally with Chlorprothixene or chlorpromazine

(b.) with osteopathic "manipulations"

(c.) with hypnosis: either by producing anesthesia or imagery or age regression.

(d.) with locum dolens placebo injections; its effects will be short-lived or long-lasting, depending on the physician's attitudes and the message he transmits through his non verbal communication. Who has not witnessed mother's kiss make the pain disappear—for ever—from the finger of her child.

I have used all these modalities except for the osteopathic manipulations and I am talking from first hand experience and not from reading a book. I hope you will deem it appropriate to publish this letter prominently, as a small contribution to correct the erroneous impressions Dr. Diggs might have created.

ALPHONSE TELFEIAN, M.D.
92 West Street
Portland, Maine 04102

In Reply:

Dr. Telfeian is looking for more in my paper on operant pain than I wanted to include. In answer to his questions, I can offer the following:

I did not attempt to establish a differential diagnosis of pain. Practicing physicians recognize depression as an associated factor of pain. Pain causes depression, and depression will increase the level of the complaint. To treat depression and not recognize operant pain might help a symptom, but not the cause of chronic pain.

The M.M.P.I. will not replace a psychiatrist or a psychologist. In a suspected case of operant pain, the M.M.P.I. is a screening procedure similar to x-ray and blood tests. An abnormal M.M.P.I. is not complete until the patient has been interviewed by a psychologist trained in its use. The point is to identify the behavioral and personality aspects of chronic sick behavior and direct the patient toward a psychological evaluation and away from surgery or endless pill prescriptions.

My paper was not meant to be a complete article on treatment modalities. Trial and error therapies will tend to treat symptoms, but, of course, can be useful in a coordinated approach when the underlying behavior pathology is understood. I would question Dr. Telfeian's opinion of placebo treatment. His example of a mother's kiss is not placebo treatment. It is an appropriate well-timed medication and treatment of choice applied in the correct strength for minor trauma to a child's finger. I do not use placebo therapy because the response is difficult to interpret. I would ask Dr. Telfeian to explain the placebo effect of a monthly B12 shot, acupuncture or disc surgery.

Referral of a patient with chronic pain to a psychiatrist may be appropriate; however, too often the patient is sent to the psychiatrist for the wrong reason. If chronic back pain is a result of motivation to receive insurance or workmens' compensation, a neurological or orthopedic evaluation with no physical impairment should be followed by a legal solution on a timely basis and does not require referral to a psychiatrist or a psychologist.

J.S. DIGGS, M.D.
Mid-Maine Medical Center
Waterville, Maine 04901

To the Editor:

I am a second year fellow in Allergy-Immunology at the University of Rochester who will be completing my training in June, 1979, and am interested in joining an established allergy practice.

My background includes board certification in Internal Medicine and board eligibility by 1979 in Allergy-Immunology.

Currently, I am looking for practices which offer predominantly adult allergy (with some pediatric allergy if necessary) and an initial salaried position, which after a one year period could develop into an associateship or partnership.

Thank you for your time and consideration.

DONALD W. PULVER, M.D.
Box 695
601 Elmwood Avenue
Rochester, N.Y. 14642

ABSTRACTS

Blood Pressure Control in Rural Maine: Results After 4 Years

N. BURGESS RECORD, M.D., Franklin County High Blood Pressure Program, Rural Health Associates, Farmington, Maine 04938; Jill Jasmin; Paul Judkins.

A multi-faceted high blood pressure program has served a population of 28,000 in rural West Central Maine during the past four years. A network of nurse-staffed, bimonthly blood pressure centers in 12 of 29 area towns provides a mechanism for screening, education, and convenient, inexpensive follow-up. Used and supported by most area physicians, program impact after 4 years has been substantial. As of June, 1978, 33,000 blood pressure checks on 11,000 individuals (50% of the over-12 population) had identified 4,082 people with possible, labile, confirmed, treated and/or controlled hypertension. Excluding patients with labile hypertension (976) and those classified as inactive (279), there remain 2,827 patients with initial confirmed hypertension. Comparing first to latest program visit for each patient, the proportion of hypertensives on treatment has risen from 56% (1594) to 73% (2061). Those with treated, well-controlled HBP has risen from 23.9% (675) to 51.2% (1449). Considering only those patients who have begun treatment with a physician, the proportion of patients with treated, controlled hypertension has increased from 42% (675/1594) to 70% (1449/2061), a degree of control which compares favorably with data reported from other successful control programs. Working in concert with primary care physicians, a regional network of community-based high blood pressure centers which emphasize education and interval blood pressure monitoring, can substantially improve rural high blood pressure control.—Presented in a poster display at the National Conference on High Blood Pressure Control in Washington, D.C. on April 4-6, 1979.

The Individual Physician: An Important Variable in Blood Pressure Control

N. BURGESS RECORD, M.D., Franklin County High Blood Pressure Program, Rural Health Associates, Farmington, Maine 04938; Jill Jasmin; Roderick Prior.

Between 1975 and 1977, a multi-faceted community program in rural Maine screened 42% (9070) of the over-12 population and identified 3708 "actual" hypertensives. Excluding labiles, the proportion with treated, controlled HBP rose in 3 years from 21% (596) to 43% (1207). In 5 (of 12) towns served, 1244 hypertensive patients identified 17 local physicians of varying specialties as their personal doctor. Total patients per doctor ranged from 3 to 168 (mean 73). Although HBP was well-controlled in 56% (691) of the group as a whole, control among physician-patient subgroups ranged from 17% to 71%. Individual physician practice habits and attitudes toward the HBP program were ascertained by self-reported physician questionnaire. An "activist" approach to BP control and a "positive" attitude toward the program correlated significantly ($p<0.05$) with degree of BP control achieved. Also, those physicians with the largest subgroup of hypertensive patients were most likely to have accomplished a high degree of HBP control ($p<0.01$). In rural Maine and probably elsewhere in the country, the proportion of hypertensives well-controlled varies substantially from physician to physician. The individual physician's attitude toward HBP and available control programs may influence the level of HBP control achieved in his/her practice. Those characteristics of individual health care providers which promote HBP control should be identified and fostered.—Presented orally at the National Conference on High Blood Pressure Control in Washington, D.C. on April 4-6, 1979.

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County Society Notes

Androscoggin

The meeting of the Androscoggin County Medical Society was held at Chase Hall, Bates College on October 19, 1978. The meeting was called to order at 8:15 p.m. by the President, Dr. Jou S. Tchao. The meeting was preceded by a social hour and dinner. There were 50 members present and three guests.

Dr. Tchao announced that the annual meeting of the Corporators would be held on November 16th instead of in December.

The minutes of the September meeting were approved as read.

Correspondence included a communication from Dr. Melvin Bacon regarding our interest in the Diabetic Program of the M.M.A.

A letter from Mrs. Monique Sullivan, President of the Association of Medical Assistants informing the group of a Guided Study Course sponsored by their Association, was read by Dr. Wolf.

Applications for active membership were approved and duly voted: Drs. Roger N. Austin, Richard E. Fortier, Jr., Betty J. Kennedy, Pierre M. LaChance, Philip J. O'Connor and David M. Walter.

Applications for junior membership were approved and duly voted: Drs. Craig E. Breese, Theodore T. Brooks, Jr., Bruce D. Alexander, Charles H. Burns, George Kunhardt, M. David Lauter, William C. Leach and Cyrus N. Walker.

It was unanimously recommended that the names of Dr. Wedgwood P. Webber and Dr. Chakmakis James be added to the list of senior members. The already approved list of affiliate members was reviewed and all were voted favorably with the exception of Dr. Merton N. Flanders who will be acted upon at the next meeting.

Motion was made by Dr. Radcliffe to establish a House Committee to arrange for a meeting place. The motion was seconded by Dr. Wolf and so voted. Dr. Lawrence Nadeau will serve as chairman, with Drs. Thomas Shields, Andre Marcotte and Leo Cousineau. The vote was 32 to 6 to continue to meet at Bates College. It, however, was left to the committee to select a convenient place.

Dr. Gilbert R. Grimes gave a detailed report of the House of Delegates' Meeting which he attended recently.

Dr. Lawrence Nadeau gave a brief report on the progress made in the matter of a Medical Education Director for the County.

Nominating Committee: Drs. Thomas Shields, Chairman, Gilbert Grimes and Gerard Morin.

It was voted to share in the Inservice Library Project.

Dr. Otis B. Tibbetts was recommended for affiliate status due to his retirement.

The meeting adjourned at 9:45 a.m.

The annual meeting of the Corporators of the Androscoggin County Medical Association was held at Chase Hall, Bates College on November 16, 1978. There were 62 members present. The meeting was called to order, following dinner, by the President, Dr. Jou Tchao.

The secretary's report was accepted as read by Dr. Wolf, the secretary.

A moment of silence was observed in respect for our departed colleague, Dr. John Busch, who passed away November 12, 1978.

Dr. Tchao read a communication from Dr. George McNeil of the Department of Psychiatry at Maine Medical Center in Portland, offering his services for a course to physicians in our County. Following discussion and a motion, it was voted not to participate in the project as there were only four votes in favor.

Dr. Lawrence Nadeau reported on the progress of the House Committee.

A Report of the Health Care Institute was given by Dr. Charles Steele and placed on file.

Comments were made by Dr. Gilbert Grimes on the discrepancy on Medicaid compensation for services to the amount of 60%.

There was a lively discussion on a motion previously tabled and removed on the matter of Second Opinion. The motion by Dr. Thomas Shields reads: I move that the Androscoggin County Medical Association adopt the policy on consultations, as stated by the Council of Medical Specialty Societies, as our reply to any inquiries regarding our position on "the second opinion question." In the policy statements regarding assisting the patient who is seeking consultation, in assuring that consultation is available, and insuring that the patient has a free choice of selecting a consultant, the individual personal physician of that patient will have the responsibility.

It was moved by Dr. Charles Hannigan and seconded by Dr. Fishman that the Association approve the motion. The vote was approved with the comment that the Association opposes FREE second opinion. The vote was unanimous.

Dr. Edmund Claxton, Jr. was presented for admission to membership. Following approval by the Councilors, he was voted to membership.

A Resolution presented by Dr. Thomas Shields was presented for consideration:

WHEREAS, the legislative processes of this nation and State have interfered increasingly with the doctor-patient relationship, the reimbursement for physicians' services, and the overall practice of medicine,

WHEREAS, the physicians of this country have thus found it necessary to become more aware of the governmental influences in the daily practice of medicine,

BE IT RESOLVED by the Androscoggin County Medical Association that the Maine Medical Association act during future legislative sessions to instruct the lobbyist for the Maine Medical Association to carefully monitor the votes of each legislator on health-related issues, particularly the issues concerning the daily practice of medicine, and report to each county medical society if their legislators voted favorably or unfavorably on these issues.

Following discussion, a motion by Dr. Kenneth Wolf and duly seconded was voted unanimously.

Dr. Thomas F. Shields reported as chairman of the Nominating Committee:

President: Dr. Lawrence A. Nadeau, Lewiston
Vice-President: Dr. Leo E. Cousineau, Lewiston
Secretary-Treasurer: Dr. Edward Z. Walworth, Lewiston
Delegates to the M.M.A. House of Delegates: Drs. Frederick C. Holler, Candace C. Walworth, Lawrence A. Nadeau, August J. Valenti and Iain D. Sanderson, all of Lewiston, and Michael V. Rynne, Auburn. Alternates: Drs. Ake Akerberg, Barry D. Chandler, Donald H. Morgan, Allan H. Ingraham, David D. Smith and Philip J. O'Connor, all of Lewiston.
Councilors: Drs. Stanley E. Rosenblatt, Gerard L. Morin and Thomas F. Shields, all of Lewiston.

Dr. Frederick C. Holler of Lewiston was designated as chairman of Delegates and Alternate Delegates for 1979.

On motion of Dr. Edward Reeves, a rising vote of thanks was given Dr. Tchao.

The meeting adjourned at 10:10 p.m.

KENNETH P. WOLF, M.D., *Secretary*

The meeting of the Androscoggin County Medical Association was held at Chase Hall, Bates College on February 1, 1979. The meeting was called to order by the President, Dr. Lawrence A. Nadeau, with 48 members present.

The minutes of the November meeting were read by Dr. Edward Z. Walworth and approved as read. Dr. Walworth gave the Treasurer's and read the Auditor's reports; both were approved as read and placed on file.

Dr. Nadeau read correspondence from the Maine Medical Association asking him to serve on the nominating committee. He accepted and asked the cooperation of the members for suggestions of candidates for offices and various committees.

A letter from the Maine Cancer Society announcing the forthcoming "Daffodil Day" in April was read and discussed. Another letter from the Women's Hospital Association was read. It is regarding the project on Nutrition which will consist of exhibits on various aspects of nutrition and material for distribution.

Applications, approved by the credentials committee, were presented by Dr. Edward Walworth and all candidates were voted



unanimously. New members are Drs. William M. Lee, Peter H. Elias, Ronald R. Campbell and Mark S. Levine.

The report of the investment committee was given by Dr. Michael J. Harkins, accepted and placed on file.

Dr. Leo E. Cousineau reported for the committee on telephone answering service. He reviewed some statistics from a recent survey. Following discussion, it was voted to continue this project.

Dr. Nadeau announced that an advisory committee would be formed with Dr. Iain D. Sanderson as chairman. Ballots with eight names were distributed to the membership with instructions to vote for four only. The following were voted to the committee: Drs. Michael V. Rynne, Stanley D. Rosenblatt, Philip J. O'Connor and August J. Valenti.

Dr. Gilbert R. Grimes reported on the meeting of the Executive Committee of the M.M.A. Among items of interest were plans for new headquarters for M.M.A. and that a new Executive Director had been hired with a three year contract.

A chart prepared by Dr. Thomas F. Shields, on the cost of meals in relation to payment of dues, was distributed and discussed. It was voted to table the matter of increase in dues to the next meeting.

A most informative talk on non-scientific healing arts was given by Dr. O'Connor.

The meeting was adjourned at 10:10 p.m.

EDWARD Z. WALWORTH, M.D., *Secretary*

York

The October meeting of the York County Medical Society was held on October 18, 1978 at the York Hospital in York. The program was as follows: Social Hour, 6:30 to 7:30 p.m., with dinner, speaker, and business meeting to follow.

After a delicious dinner, Dr. Maurice Ross spoke on matters relative to the Maine Medical Association which were of concern to us all. His material included progress made by the Building Committee of the Maine Medical Association. It was decided to have this newly proposed building in the Augusta area; this to have its headquarters in the area of the Civic Center in Augusta. This has good property prospects. There are other organizations that are interested in having office space in such a building. The Maine Medical Association is prepared to spend $35,000 for this plot of land. The estimated cost of the building will be between $200,000 and $300,000. This was based on 1978 figures, but the cost in 1979 may be a little higher. The estimated cost per square foot could be from $29 to $49 per square foot; this depending upon the type of construction desired. However, nothing further will be done before the next meetings of the House of Delegates to be held in December and April.

Another item included the report of the Search Committee, as Dan Hanley plans to retire shortly.

Another item of importance was the opinion of our President and others who feel that it is very important for us as physicians to contribute to some of our political candidates who might be helpful to the cause of physicians in general. It was urged that all of us contribute to the appropriate type candidates.

There is another committee working under the chairmanship of Dr. John Knowles of Portland. He is very much interested in dealing with the impaired physicians in a way as to be helpful to their cause.

He also gave examples of our Federal bureaucracy and gave some insight as to what is going on with the Maine Medical Mutual Insurance Company, which appears to be doing well. He also brought to light some of the "goings-on" with the Maine Hospital Association and stated that they had hired a woman to secure certain information at a salary of $35,000 per year. He also gave examples of certain incidents going on in Maine where there was an inconsistency whereby certain things could have been done in local areas but were sent to other parts of the State where there was a savings of only a very few dollars. He discussed other items which were of lesser importance and need not be mentioned at this time.

Following this, a most interesting program entitled "The Blue Shield Story" was presented. Among the topics discussed were: 1) Background and history; 2) Blue Shield as a business entity; 3) Realities of the market place; and 4) Issues, etc. The presenters of these topics were: George Hansen, Vice President of Finance; Max

Powell, Vice President of Marketing; Frank Faherty, Vice President of Research and Provider Affairs. Our president, Dr. Hazzard, introduced Mr. Frank Faherty, who was the first presenter of the program. The program lasted about an hour.

The minutes of the last meeting were dispensed with in the interest of time. There was no old business.

New business included applications for membership to the York County Medical Society: Drs. Thomas E. McDermott, David L. Massanari, Richard S. Tockman and Bertrand J.M. Duval-Arnould. They were duly elected into membership.

Announcements:

1. Plans for the Diabetes Program for York County were announced. It is worthy to mention at this point that the Diabetes Program in Maine has attracted national interest.

2. The January meeting of the York County Medical Society will be held on January 10, 1979. Place to be announced. This is the Annual meeting.

3. Memorials: Mrs. Kenneth E. Leigh, American Cancer Society; Mrs. Lawrence Hazzard, American Heart Association; Mrs. Mirle Kellett, New England Deaconess Hospital, Oncology Department; and Dr. Robert Downing, Maine Arthritis Association. There was a moment of silence in respect to our Colleague and to the wives of our Colleagues.

4. The Fall meeting of the House of Delegates of the Maine Medical Association to be held December 9, 1978 at the Mid-Maine Medical Center, Waterville, Maine.

Correspondence:

1. Request from the American Medical Association for nominations to fill the vacancy in the Council on Constitution and Bylaws created by the death of E. M. Satulsky, M.D., to fill the unexpired term ending June 30, 1980. Any members of the Society interested in this or other Council vacancy of the American Medical Association should contact the Society for applications.

There was no miscellaneous business.

This was another disappointing turnout, with eleven physicians and five guests in attendance.

The meeting was adjourned at approximately 9:50 p.m.

MELVIN BACON, M.D., *Secretary*

Kennebec

The Kennebec County Medical Association met at Guido's Wine Cellar on November 16, 1978, with 42 members and 4 guests in attendance.

After a very pleasant social hour and a delightful meal, the President called the meeting to order at about 8:15 p.m.

There was correspondence in the form of a news release from HEW concerning Medicaid utilization regulations.

There was no old business.

The applications for membership of Drs. Richard Hobbs, John Meyer, Bhagavan Maganti were read for the first time.

There being no further new business raised, Dr. Moore introduced Mr. Frank Faherty, the Vice President of the Provider and Professional Relations for Maine Blue Cross and Blue Shield, who proceeded to present a program outlining the structure of Blue Cross and Blue Shield as a business entity and some of the factors that were involved in the way that Blue Shield functions in the market place and some of the future thrusts of the Blue Cross and Blue Shield programs. There were several questions from members concerning specific points of discussion, and in general, it was a good exchange between the Blue Cross and Blue Shield people and the members of the Association.

The meeting was adjourned at 9:45 p.m.

The Kennebec County Medical Association met at the Silent Woman Restaurant in Waterville on December 21, 1978, with the wives attending with the members.

The business meeting was very short and was limited to a vote on the applications of Drs. Richard Hobbs, Bhagavan Maganti and John Meyer. All of these gentlemen were accepted into the membership with a unanimous vote. The application of Dr. Wayne P. Halfar was read for the first time.

Dr. Moore then introduced our speaker, Mr. George Smith, who presented a most interesting account of an expedition climbing Mt. Katahdin in the winter, which was enjoyed both by the members and their wives.

O. THOMAS FEAGIN, M.D., *Secretary*

Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges Inn in Wiscasset, Maine on November 21, 1978.

There were twenty-six members and guests present. The meeting was called to order by the President, Dr. Aldo F. Llorente; the minutes of the October meeting were approved as read by the secretary.

Dr. Leck then introduced Drs. Maxwell and Dowling, of Cumberland County, who spoke for Medical Mutual Insurance Company of Maine, with corroborative comments by Dr. Daniel Hanley.

The Board of Censors recommended for approval the application for active membership of Dr. Daniel H. Wood of Bath. The membership unanimously accepted the nomination.

Dr. Bostwick introduced Mr. David Broadbent, of the Preschool Screening Program based in Boothbay Harbor, who described his proposed program coordination of screening for handicapped children. Much discussion of the validity of screening programs followed.

Dr. Llorente appointed a nominating committee of Drs. Schall, Avantaggio and Burden to bring a slate of officers for election at the December Annual Meeting.

The meeting was adjourned at 10:00 p.m.

The Annual Meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges Inn in Wiscasset on December 19, 1978, with 36 members and guests present.

The meeting was called to order by the President, Dr. Aldo F. Llorente; the secretary read the minutes of the November meeting, and they were accepted as read.

The treasurer proposed that the 1979 annual dues be set at fifty dollars. The motion was made, seconded, and passed.

The report of the nominating committee was read, and two nominations were made from the floor for positions unfilled by the committee. The motion was then made that the nominations be closed and that the secretary cast one ballot for the following slate:

President: Dr. P. Richard Cote, Bath

Vice-President: Dr. Frank O. Avantaggio, Jr., Damariscotta

Secretary-Treasurer: Dr. George W. Bostwick, Newcastle

Delegates to the M.M.A. House of Delegates: Drs. Richard Evans, III, Gerry S. Hayes and Louis Bachrach, all of Brunswick. Alternates: Drs. Frank W. Sheldon, Wiscasset, Douglas G. Long, Boothbay Harbor and Edward C. Schmidt, Brunswick

Censors: Drs. Frank O. Avantaggio, Jr., Damariscotta, Carl R. Griffin, Jr., Boothbay Harbor and Elihu York, Brunswick

Program Committee: Drs. Daniel H. Wood, Bath and John S. Van Orden, Brunswick

Representative to Health Care Finance Committee: Dr. Louis Bachrach, Brunswick

The motion was passed, and the secretary then introduced Dr. George McNeil, of Portland, who spoke on Depression.

The meeting was then adjourned.

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held on January 16, 1979 at The Ledges Inn, Wiscasset, with twenty-nine members and guests present.

The minutes of the December meeting were read by the secretary after the meeting was called to order by the President, Dr. P. Richard Cote, and the minutes were accepted as read.

There was no old business.

Dr. Wood announced for the Program Committee that the 1979 theme would be Emergencies in Practice.

Dr. Richard Evans discussed the December interim meeting of the M.M.A. House of Delegates: the proposed headquarters building, BC/BS negotiations, and lobbying activities in Augusta. Dr. Leck spoke further on these matters, and general discussion followed.

Dr. Wood then spoke on Endocrine Emergencies.

GEORGE W. BOSTWICK, M.D., *Secretary*

Penobscot

The November meeting of the Penobscot County Medical Society was held on November 21, 1978 at the Red Lion in Bangor. About sixty members attended. In addition to this, five guests of the County Medical Society from Associated Hospital Services of Maine (Blue Cross/Blue Shield), were present as featured speakers.

The meeting was opened by the President, Dr. David S. Beebe and the minutes of the October meeting were approved without addition or change. Following this, Treasurer Dr. Michael Solomon reported on the financial status of the Society, which presently has monthly expenses of approximately $800.00. Dr. Beebe then discussed the proposed listing of the physicians accepting new patients under a County Medical Society number, and indicated that this could be updated on a quarterly basis. Once again interested members were encouraged to volunteer for the committee charged with developing a Physicians Directory for Penobscot County. Dr. Beebe emphasized that greater input was necessary from the membership in order to help determine the future course and activities of the Society in light of the changing medical and political environment.

As noted in our newsletter of October, comments and suggestions by the membership may be included on the postcard returned to the County Secretary before each meeting.

Mr. Frank Faherty, Mr. George Hanson and Mr. Max Powell, of Associated Hospital Service of Maine, then discussed the structure and function of the Maine Blue Cross and Blue Shield and in addition to this outlined various directions in which that organization intended to proceed. After their presentation, they answered questions from the Society membership. There being no further business, the meeting was adjourned at about 9:30 p.m.

The December meeting of the Penobscot County Medical Society was held on December 19, 1978 at the Penobscot Valley Country Club. About forty-eight members attended, in addition to our featured speaker, Dr. George Pauk and Mr. Thompson, the Hospital Administrator for St. Joseph Hospital.

The meeting was opened by the President, Dr. David S. Beebe and the minutes of the November meeting were approved without addition or change. Dr. Beebe spoke briefly about the upcoming January meeting and the decision to forego a speaker on that occasion. It was felt that by decreasing the number of guest speakers over the course of the year more time could be devoted to discussion of Medical Society business. The application of Dr. Fred M. Wlodarski was read. He was unanimously elected to membership by written ballot.

Dr. George Pauk, Director of Family Nurse Associate Program at Maine Medical Center, then discussed the qualifications and training of the Family Nurse Associate. His presentation generated several interesting questions and comments from the membership. The program is apparently funded primarily by the Federal Government with some additional state funding. Dr. Pauk indicated that about 99% of the Nurse Associates work for physicians rather than engage in independent practice. Information concerning the Nurse Associate's role: legal responsibility, and projected utilization within the medical community was understandably less than definite.

The meeting was adjourned at about 9:30 p.m.

JAMES R. CURTIS, M.D., *Secretary*

Washington

A regular meeting of the Washington County Medical Society was held at the Wickachee Inn, Calais, Maine on November 21, 1978, with seventeen members and guests present.

Dr. James C. Bates of Eastport, Maine, President of the Washington County Medical Society, introduced Dr. Francis Kittredge of Bangor, President of the Maine Medical Association.

1. Dr. Kittredge stated that in negotiating for a fee schedule with the Dept. of Human Services, a federal judge ruled that there was no violation of the Sherman Anti-Trust Act.

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THE NAL of The Maine Medical Association

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John W. Wickenden, M.D., Rockland	Third District—Lincoln-Sagadahoc, Knox	1980
O. Thomas Feagin, M.D., Augusta	Fourth District—Kennebec	1981
David L. Phillips, M.D., Rumford, *Executive Committee Chairman*	Fifth District—Franklin, Oxford, Somerset	1979 1979
Harold E. Knuuti, M.D., Belfast	Sixth District—Hancock, Washington, Waldo	1979
Gilbert R. Grimes, M.D., Lewiston	Seventh District—Androscoggin	1980
Charles H. Lightbody, M.D., Guilford	Eighth District—Penobscot, Piscataquis	1980
Harry M. Helfrich, Jr., M.D., Presque Isle	Ninth District—Aroostook	1981
Richard C. Leck, M.D., Bath	Past President	1980
Douglas R. Hill, M.D., South Portland	Past President	1981
Robert E. McAfee, M.D., Portland	Delegate to the AMA	Dec. 31, 1979
Brinton T. Darlington, M.D., Augusta	Alternate Delegate to the AMA	Dec. 31, 1979
Harry A. Bliss, M.D., Portland	Ex-Officio	1979

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Preliminary Study of the DES Exposed Female in Maine

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Since the 1970 article by Herbst[4] linking intrauterine exposure to Diethylstilbestrol (DES) with the subsequent appearance of vaginal and cervical adenocarcinoma in the offspring, the need to identify and screen exposed individuals has become apparent. Estimating that between 5,000 and 15,000 young females residing in Maine were so exposed,[1,2] a DES Registry Program was established for this purpose by the American Cancer Society, Maine Division, in 1974. To date, five cases of clear cell adenocarcinoma of the cervix or vagina have been diagnosed in Maine; of these, four have had a definite association with DES in utero. Concerned by the occurrence of these carcinomas in young women, the authors have reviewed their records to identify these DES exposed individuals.

We agree with Edinger[2] who, in an earlier article describing the DES screening program in Rhode Island, stated that a paper of this sort should not attempt to review the literature concerning DES or its associated malignant or nonmalignant changes. Rather, our purpose will be to inform the practicing physicians in Maine of our observations to date in the DES exposed females and to suggest steps to be followed in their continued evaluation.

Materials and Methods

Between February of 1974 and February of 1979, a total of 203 patients were seen either in our private practice or under our supervision at the Colposcopy Clinic, Maine Medical Center. Pertinent data was gathered. History of DES exposure was obtained whenever possible by review of records and obtaining relevant information from the patient or her mother. Documentation through review of old records was difficult and therefore in the presence of gross vaginal or cervical abnormalities compatible with DES exposure, the patient was considered as having a presumptive history of exposure to DES.

Thorough pelvic examination was performed. Included in the examination were: 1) careful palpation of the anterior and posterior vaginal walls, 2) direct visualization of the cervix and vaginal tissue, 3) obtaining of appropriate Pap smears, 4) use of half-strength Lugol's solution to stain the vagina and cervix, 5) colposcopic examination, and 6) appropriate biopsies as indicated.

Colposcopy was always accompanied by the completion of a "colposcopic map" (Figure 1) patterned after a form developed by R. Richart of Columbia Presbyterian Hospital (NYC). This has proved to be most useful enabling an adequate record to be continually updated on each patient as these "maps" are completed at the time of each colposcopic examination to ascertain changes on the cervix and vagina. Symbols for various colposcopic patterns noted, i.e., "mosaic," "punctation," keratosis," "transformation zone," and "columnar epithelium," are those recommended by the American Society of Colposcopy and Colpomicroscopy.[9]

Biopsies were obtained to document abnormal findings as seen grossly and/or colposcopically. These biopsies were taken using either the Jako laryngeal biopsy forceps or the larger Eppendorpfer forceps (Photo 1). The former is an ENT instrument

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adopted for gynecologic and colposcopic use as suggested by T. Sanford.[7] When indicated endocervical curettage was obtained using Duncan curette. Specimens were initially placed in a 10% formalin solution; these were imbedded in the customary manner and stained with hematoxylyn and eosin. Multiple sections from each block were taken for examination. All Pap smears and biopsies were reviewed by the authors, two of whom (MEF and JZ) are gynecologists, the third (LT) a pathologist.

Results

At the time of initial examination, the 203 patients ranged in age from 10 to 32 years (Table A) with a median of 23.6 years and a mean of 20.4 years. The age groups of 16-20 years and 20-25 years accounted for the greater number, totalling 154 individuals. The date of birth of these individuals corresponded to the time of greatest DES usage—the late 1940's through the next decade. Interestingly, we feel the we are now evaluating patients at an earlier age, probably due to the increased awareness on the part of the medical profession and the public in general regarding DES.

One hundred and sixty-four of 203 were private patients; the remaining 39 were seen in the MMC Colposcopy Clinic. The manner of entrance to our survey group was noted. Seventy-two patients were direct physician referrals; 67 were self-referred as they had been told of DES exposure; finally, 62 patients knew initially of no DES exposure but were found by the authors to have pelvic changes compatible with same. For history to be considered "absolute for DES exposure," a copy of the prenatal chart dealing with the patient's gestation was considered mandatory. This, however, was obtained in only 18 individuals and we have accepted information from physicians, patients, their mothers, and finally examination itself as indicative of in utero DES exposure. This concept has been advised by others.[10]

We have found these DES exposed females to have attained a high scholastic level. Of the 169 whose educational history is known, the number continuing their education beyond high school is remarkable (Table B). Many are either in college, have graduate degrees, or are attending school beyond the twelfth grade level. Periodic group meetings held by the authors and their patients along with members of the patient's family and other interested individuals have proved to be of great value for all involved. Thus patients have been able to actively participate in their own education relative to DES and its associated findings.

One hundred and ninety-four females have been fully examined. This includes: 1) bimanual pelvic ex-

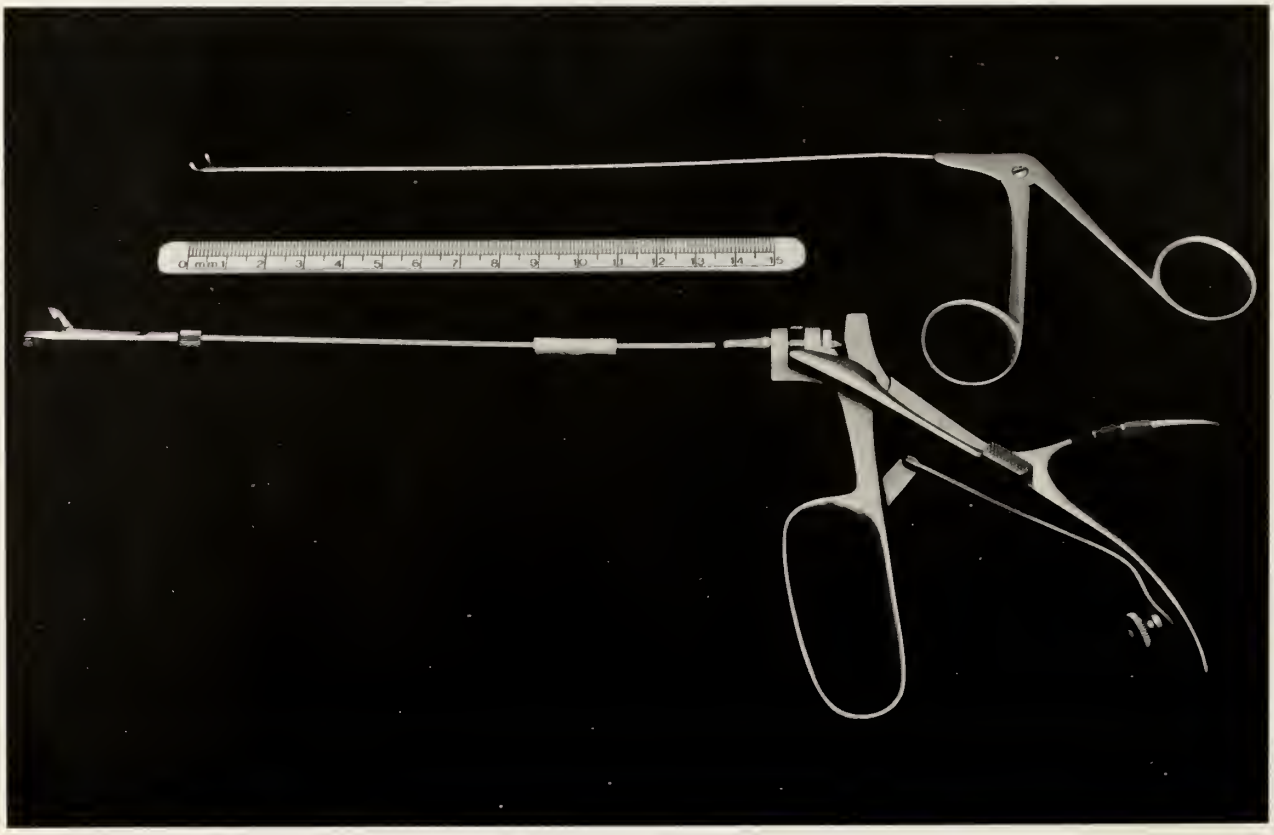


Photo 1

Upper instrument; Jako laryngeal biopsy forceps made by Piling Company and adopted for colposcopic use.

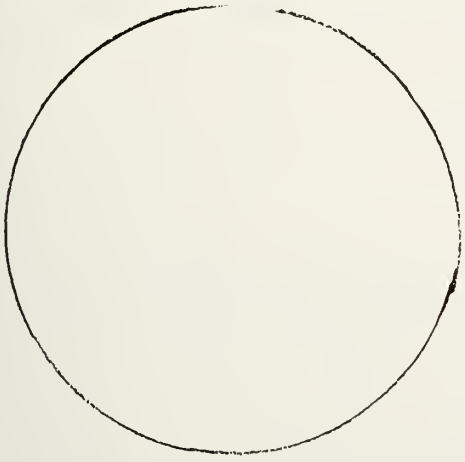
Lower instrument; the Eppendorpfer cervical biopsy forceps.

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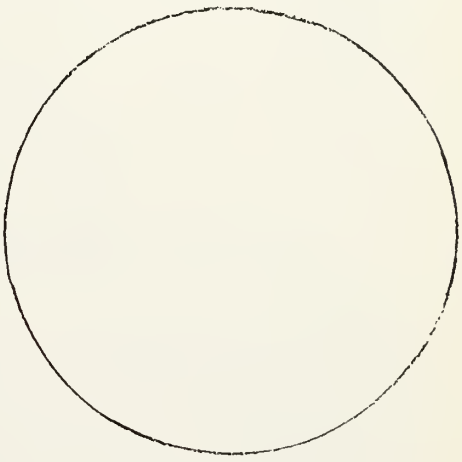
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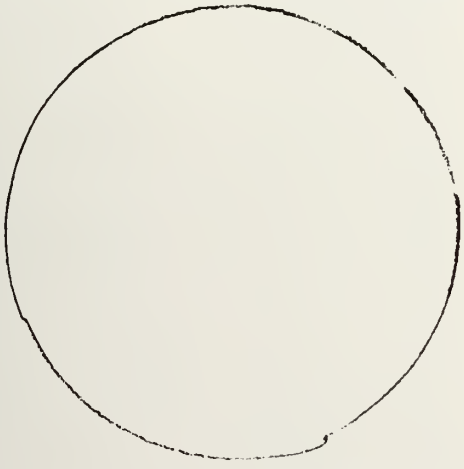
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COLPOSCOPY:



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NOTES:

Smear Diagnosis:

Biopsy Diagnosis:

Lugol's 1/2 strength solution

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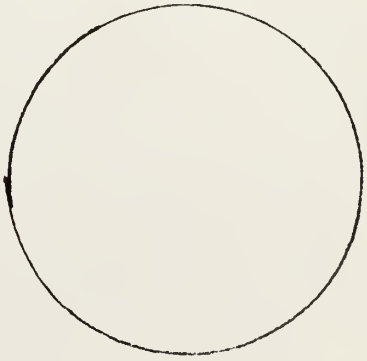


FIG. 1

Table A

Age at First Examination

Age	*# Pts.*
13 years or less	2
14-15 years	10
16-20 years	66
21-25 years	88
26-30 years	36
31 + years	1
Total	203

Table B

Scholastic Level at Time of First Examination (169 Pts.)

Schooling	*# Pts.*
Presently attending high school	21
High school graduate	38
College student	43
College graduate	34
R.N./Student nurse	15
Other post high school education	19
Total	169

Table C

Cervical and Vaginal Abnormalities Found at First Examination

Type	*# Pts.*
None noted	14
Gross tumor	2
Granular "strawberry" cervix	101
Polypoid/pseudopolypoid cervix	16
Pericervical collar	43
Cockscomb	40
Recessed/foreshortened cervix	36
Irregular os	107
Transverse vaginal ridge	1
Other	11

Table D

Cytologic Abnormalities Found in DES Exposed Patients

Type	*# Pts.*
Inflammation	28
Metaplastic epithelial cells	2
Atypical endocervical cells	3
Dysplasia, mild	12
Dysplasia, moderate	5
Dysplasia, severe	2
? severe dysplasia/? CIS	1
Total	53

amination, 2) obtaining cervical, vaginal and endocervical Pap smears, 3) colposcopy with completion of a colposcopic map, 4) Lugol's staining of the vagina and cervix, and 5) biopsies when indicated. Nine patients are still in the process of evaluation. Seventeen patients were examined under anesthesia; the majority being performed at the beginning of the study when our experience was not as great. In the initial two years, 1974-75, seven examinations under anesthesia were performed by the authors. Since then, however, we have needed general anesthesia once in each succeeding year and then only in very young individuals having signs and symptoms sufficiently alarming to warrant immediate examination and deemed possibly only under general anesthesia. Six of these seventeen examined under anesthesia were performed by physicians other than the authors and were referred for follow-up.

Fourteen of 194 patients had normal pelvic exams (Table C). Abnormalities were observed in the remainder. The granular or "strawberry" cervix was seen in 49% of the patients (colposcopy showed this to represent exocervical columnar epithelium and/or squamous metaplasia). Polypoid and pseudopolypoid changes of the exocervix (7%), cockscomb (19.6%), and pericervical collars (21.5%) were also present. The two patients having clear cell adenocarcinoma had grossly visible lesions; the first, located on the anterior vaginal wall, measured 3 x 4 centimeters; the second had a circumferential 3 x 3 centimeter cervical lesion.

Classically the os in a normal nullipara is described as a "small aperture usually circular (and located) in the center of the portio vaginalis;"[5] with pregnancy, labor and delivery the os becomes open, larger and transverse. However, the cervical os in DES exposed patients has been markedly unlike the preceding description. Eccentric placement with transverse, vertical, oblique or irregular cervical ossa had been noted in over 40% of nulliparous individuals.

Following gross inspection, colposcopy and Lugol's staining were performed. Interestingly, seven exams normal to gross and colposcopic exam exhibited lack of iodine staining in the upper portion of the vagina. This reflects nonglycogenation of the squamous cells in the area, often a characteristic of DES exposed vaginal tissue. Thus, Lugol's staining must be considered an integral part of DES evaluation.

Cytology was interpreted as abnormal in approximately 25% (Table D). This excluded the two cases of clear cell adenocarcinoma. Inflammation was present in 28 of 53 patients; atypia or dysplasia of various degree was noted in 23. The majority of dysplastic Pap smears represented milk dysplasia (12) and only three suggested severe dysplasia or carcinoma in situ. Colposcopically, abnormal cervical and/or vaginal patterns of mosaic and punctation were seen to a degree in the majority of patients (approximately 80%). Adenosis was observed and documented with positive biopsy in 43% (Table E). The diagnosis of adenosis was accepted only when columnar epithelium was present microscopically on

Table E

Pathology in DES Exposed Individuals

Microscopic Dx.	# Pts.	Biopsy Site Vaginal	Cervical
Adenocarcinoma	(2)	1	1
Adenosis	(85)	85	0
Microglandular Hyperplasia	(6)	0	6
Mild Dysplasia	(23)	9	14
Moderate Dysplasia	(13)	1	12
Severe Dysplasia	(5)	1	4
CIS	(3)	0	6
Total	(137)		

Table F

Obstetrical History — 76 Pregnancies

Outcome		# Pts.
Voluntary termination		20
Undelivered		3
Ectopic pregnancy		1
Stillborn (21 wks. gestation)		1
Spontaneous abortion		6
Vaginal Delivery:	32-36 wks.	3
	36-38 wks.	3
	38-42 wks.	29
	unknown date	2
Cesarean Section:	CPD	3
	PROM with breech	2
	Breech, term	1
	Repeat	3

the vaginal tissues; columnar epithelium of the cockscomb or other portion of the cervix was not interpreted as adenosis. Additionally, the presence of vaginal squamous metaplasia microscopically was not accepted as evidence of previously existing adenosis; again, definite evidence of a columnar type epithelium needed to be seen histologically in order for the diagnosis of adenosis.

Abnormal cervical or vaginal biopsies were obtained in 137 specimens (Table E). However, 85 were of adenosis, as mentioned above; 2 others showed clear cell adenocarcinoma, of which one originated on the cervix, while the second was of vaginal origin. Six examples of microglandular hyperplasia of the cervix were found. The remainder (44) demonstrated dysplasia of varying degrees (41) or CIS (3). Eleven biopsies of vaginal tissue showed mild or moderate dysplasia; there were no instances of vaginal severe dysplasia or CIS. However, of 33 cervical biopsies showing dysplasia, 4 demonstrated a severe dysplasia and 3 CIS

Discussion

Of concern has been the high percentage of dysplasia noted on cervical and vaginal biopsies in our series. An abnormal rate of 21% is above the expected although another study, recently reported, had similar results.[3] However, others such as Townsend[10] have reported a lower prevalence rate. Therefore, this report wishes to alert physicians in Maine to the situation of an abnormal biopsy occurring in DES exposed individuals and to suggest consultation be obtained with other more experienced individuals prior to any therapy being initiated. Our own slides are being forwarded to representatives of "The Registry for Squamous Neoplasia of the Vagina and Cervix in the DES Exposed Female." Only once consultation has been obtained should therapy, i.e., cryocauterization or excisional biopsy, be considered.

Finally, our survey of DES patients led us to review obstetrical history in these individuals (Table F). While the majority of surveyed patients were nulliparous (153 of 203), a total of 50 individuals have conceived. Seventy-seven pregnancies have been recorded. Of these, 20 pregnancies were voluntarily terminated because of patient preference. One ectopic pregnancy and one stillbirth at 21 weeks were noted. A spontaneous abortion rate of 10.5% (6 of 57) was well within normal limits. Three patients are still pregnant. Forty-six infants have been delivered, 37 vaginally and 9 via Cesarean section. The majority of vaginal deliveries occurred at term and were uncomplicated. Two patients have had cerclages placed; both were removed and vaginal delivery occurred near term. The primary section rate of 13% compares favorably with the general non-DES exposed population. The indications for primary Cesarean section were: 1) breech presentation at term (1 patient), 2) premature rupture of membranes with breech presentation (2 patients, one at 32 and the second at 33 weeks), and 3) cephalopelvic disproportion (3 patients). The remaining three were performed for repeat Cesarean sections.

Until this point no discussion of adenocarcinoma has occurred. Yet the authors have seen two cases of this disease. Three others are known to have occurred in Maine.[1,12] We mention this only to emphasize the fact that a large number of DES exposed females are present in Maine, as yet unexamined or unrecognized. The incidence of DES associated adenocarcinoma is reported as anywhere between 0.4-1.4 per 1,000 exposed population. Five individuals have already been identified in Maine. Extrapolating from these five patients with disease, it is possible that 5,000 to 50,000 individuals are involved; hence the thought that between 5,000 and 15,000 DES exposed females are present in our State is not inconceivable. Therefore, careful questioning of all females between 10 and 30 years of age regarding DES exposure becomes mandatory. Thorough examination must then be performed with careful observation and description of any abnormality found. Consultation is encouraged, especially when a physician is not familiar with the unique findings observed in these individuals.

The long-term effects of DES are not yet known; follow-up evaluation is extremely important. Stafl[8] has voiced concern that a large area of squamous metaplasia existing in areas of adenosis may predispose to the development of squamous cell neoplasia. A similar concern is voiced by Veridiani[11] and his group.

Furthermore, clear cell adenocarcinoma may develop in the vagina or cervix after complete and thorough initial evaluation. Anderson[1] has reported a case of this sort. The patient was treated surgically with radical hysterectomy, vaginectomy, para-aortic and pelvic lymphadenectomy, and vaginal reconstruction; she has shown no evidence of disease at one year follow-up. Another individual, after negative initial complete evaluation, was referred to us with proven vaginal clear cell adenocarcinoma. Unfortunately at exploration she was found to have tumor already involving the right common iliac nodes and expired within a year because of metastatic disease. Interestingly, both these patients were from Maine and were diagnosed within the past two years.

In summary, for the better care of these DES exposed individuals important points to emphasize are: 1) identification, 2) complete initial evaluation, 3) consultation when indicated, and 4) long-term follow-up. Discussion with the patient regarding her concerns and fears is an important factor that must always be considered. Tentative reassurance may be given to the patient regarding future conceptions as in this small series the successful outcome of pregnancy was comparable with non-DES exposed individuals.

Acknowledgments

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PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.
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E R C P

The First 100 Cases

Irving J. Poliner, M.D.* and Julia Foley, R.N.**

Endoscopic Retrograde Cholangio-Pancreatography (ERCP) is almost 10 years old although it has been in general use in this country for only 4 to 5 years. Two and one-half years ago it was first performed at the Mercy Hospital by this physician. A preliminary report appeared in *The Journal of Maine Medical Association* in 1977.[1] Recently the 100th ERCP was performed by this physician at the Mercy Hospital. This is the largest series in Maine and it appears appropriate to report it.

ERCP is indicated in the following situations:

1. for biopsy of a lesion at the ampulla of Vater
2. for collection of pancreatic secretions for cytodiagnoses or for physiological studies
3. for visualization of the pancreatic ductal system for inflammation, obstruction, cancer, stones or cysts
4. for differentiation of extra-hepatic and intrahepatic jaundice
5. for clarification of the cause of extra-hepatic jaundice, i.e., tumor vs. stone
6. for visualization of the gallbladder and/or gallstones
7. for manometric measurements of the Sphincter of Oddi
8. for evaluation of unexplained upper abdominal pain
9. and finally for Endoscopic Retrograde Papillotomy (ERP) and removal of common duct stones

While other procedures (abdominal sonography, abdominal computerized axial tomography, abdominal angiography, and percutaneous transhepatic cholangiography) may be helpful, none have the diagnostic versatility or therapeutic ability of the ERCP and ERP. Additionally they may represent expensive equipment (sonography $60,000, CAT $400,000), invasive risks such as bleeding and bacteremia, or may be contradicted by bleeding and clotting disorders.

Initial reports[2] suggested a high incidence of failure and of complications. It quickly became apparent that failure and complications occurred "early on" and in "inexperienced hands."[2] If the Mercy Hospital series is separated into "first 50" and "second 50", this has been found to be true. With experience the procedure has been successfully performed in 15 minutes without complication.

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Instrumentation and Technique

The Olympus model JF-B2, side viewing, fiberoptic duodenoscope and a standard teflon catheter, 1.7 mm in the external diameter, were used. Demerol® , Valium® , atropine and glucagon were given. After passing the instrument into the duodenum, the ampulla of Vater was usually found on the posterior medial wall, 4 to 6 cm, beyond the pylorus. If it could not be cannulated on insertion, it was cannulated by "hooking and withdrawing the instrument." The patient lay on his left side and was rolled prone if necessary. Renografin® -60% was used. Two to 5 ml was injected into the pancreatic duct slowly with advice from the radiologist. The biliary tree was filled with sufficient dye to adequately outline all the ducts and the gallbladder. Fluoroscopic evaluation and radiological documentation was performed by members of the radiology department. A delayed film, 15 minutes after injection was frequently helpful.

Results

In the first 50 cases, there were 14 unsuccessful cannulations. Two were patients with a Bilroth II anastomosis and three were due to equipment failure. Nine of forty-five or 20% were unsuccessful due to physician's inexperience. In the second 50 cases, there were four unsuccessful cannulations. In one, the ampulla was inside a duodenal diverticulum. In a second, the ampulla was cannulated for 3 mm, but there was an obstruction. Two of forty-eight or 4% were truly unsuccessful. This 4% failure equals the average reported from large medical centers. In the first 50 cases, when cannulation occurred, both ducts were visualized 42%. In the second 50 cases, cannulation of both ducts occurred 53%. This is slightly less than reported by large centers.

An attempt was made to determine the diagnostic usefulness of this procedure. It became obvious that a "negative" test was helpful although not to the same degree as a "positive" finding. Elimination of a number of possible diagnoses was helpful in itself. For this reason, I feel that the procedure is helpful regardless of the findings or failure to cannulate the primary duct. Positive findings have been cancer of the pancreas, pancreatitis, pancreatic cyst, common duct stone, benign and malignant strictures of the common duct, cystic duct stone, and gallstones.

Complications

There were no deaths in this series and no complications requiring surgery. In the first 50, there was one case of post-cannulation pancreatitis, i.e, ab-

Continued on Page 238

Endoscopic Retrograde Papillotomy

Irving J. Poliner, M.D.,* Laurie Murray** and Monique Curtis***

Endoscopic Retrograde Papillotomy (ERP) was a natural development following Endoscopic Retrograde Cholangio-Pancreatography (ERCP). This endoscopic electro-surgical technique has become an alternative to operative sphincterо-plasty or common duct exploration for the treatment of common duct stones and papillary stenosis. Initially it was developed in Germany and Japan in 1974. In 1976, it was introduced into the United States. The technique is similar to ERCP.[1] One must be certain, however, that the cutting wire is selectively in the common duct and oriented in the "11 o'clock" position.

This technique became available and was first used by the Mercy Hospital Gastrointestinal Service in 1978. It has been used on three patients. Since these three patients are a "first, in Maine" it seems appropriate to report them in this journal.

Case Reports

Case 1. Mercy Hospital #269-890. This 83-year-old white male was referred from a small hospital for evaluation of abdominal pain and jaundice. He had severe chronic obstructive pulmonary disease and had had a previous episode of respiratory failure. Past history also showed arteriosclerotic heart disease with old myocardial infarction and angina pectoris, and a cholecystectomy for cholelithiasis in 1954. Physical examination showed a chronically ill, elderly, white male. His temperature was 38° C. His sclerae were minimally icteric. There was evidence of COPD and generalized arteriosclerosis. The heart sounds were faint, but normal. The liver was enlarged, but not tender or nodular. The spleen was enlarged, also. Laboratory data showed a normal blood count, prothrombin time and partial thromboplastin time. The total bilirubin was 2.1, alkaline phosphatase 1175, gamma GT 750, and SGOT 113. Blood cultures grew E. Coli. Pulmonary functions showed severe airway obstruction. An electrocardiogram showed an old anterior wall myocardial infarction. The E. Coli bacteremia was treated and cured with gentamycin and ampicillin.

On 6/23/78, an endoscopic retrograde cholangiopancreatography (ERCP) showed an obstructing common duct stone. The family and the patient expressed strong desires to avoid surgery. After carefully explaining the risks involved, endoscopic retrograde papillotomy (ERP) was performed on 6/27/78. On 7/5/78, an ERCP showed the stone to be present. On 7/10/78, an ERCP was performed again and showed the common duct stone. On 7/13/78, an ERP was performed for the second time. The technical difficulties of the ERP were great, and it was felt wise to open the ampulla gradually. The patient was discharged on 7/17/78. Since then he has felt well, gained weight, and has had no jaundice or fever. He has been unwilling to return to the hospital for a repeat ERCP.

Case 2. Mercy Hospital #269-554. This 73-year-old white female was transferred on 7/13/78 to the Mercy Hospital for an ERP. She had been admitted to a large nearby teaching hospital on 7/4/78 for evaluation of jaundice. An ERCP on 7/7/78 showed 4 common duct stones. A cholecystectomy for stones had been done in 1955. The equipment for ERP was not available at the first hospital and she was therefore transferred. Past history also showed a previous "heart attack." Angina pectoris occurred with effort and she took 1 to 3 nitroglycerin tablets daily and Lanoxin® 1 tablet daily. Physical examination showed a pulse of 54. Bruit were heard over both carotid arteries. The heart was enlarged with a Grade II apical systolic murmur. The abdominal examination was normal. There was no visible jaundice. Laboratory data showed a CBC, prothrombin time, and partial thromboplastin time to be normal. The bilirubin was 1.4, alkaline phosphatase 530, and SGOT 59. An electrocardiogram showed left ventricular hypertrophy and an old inferior myocardial infarction. After carefully explaining the risks involved, an ERP was performed on 7/14/78. She had no complications and was discharged on 7/16/78.

On 7/26/78, as an out-patient, an ERCP was performed for re-evaluation. The stones were still present. The papillotomy wire was immediately inserted and a repeat ERP was performed. She was admitted to the hospital for observation afterwards. She remained asymptomatic and was discharged the following day. She has been unwilling to have further diagnostic studies since she feels "well." On 2/21/79, an SMA showed a normal bilirubin, cholesterol, total protein, albumin, globulin and SGOT. Her alkaline phosphatase was 136 (normal 30-115). We believe the stones have passed.

Case 3. Mercy Hospital #273-314. This 77-year-old white male was admitted to the Mercy Hospital on 12/6/78 for treatment of common duct stones and jaundice. He had been admitted to another hospital 1 week prior for jaundice. The day of admission he came to the Mercy Hospital for percutaneous transhepatic cholangiography (PTC). This demonstrated two common duct stones. The problem was discussed with his physician. It was decided to transfer the patient to the Mercy Hospital for an ERP or cholecystectomy and common duct exploration. Physical examination showed an elderly, jaundiced, white male. The abdominal examination was normal except for a small reducible umbillical hernia. Laboratory data showed a CBC, prothrombin time and partial thromboplastin time to be normal. Bilirubin was 6 (direct 4.3), alkaline phosphatase was 280, SGOT was 120. The patient expressed strongly the wish not to have surgery. The risks of ERP were explained and he agreed to this procedure. On 12/7/78, an ERP was performed without difficulty. On 12/14/78, an ERCP was done; the two common duct stones were still present. The papillotomy wire was immediately inserted and the sphincterotomy was enlarged. He had no difficulties from the ERP and was discharged on 12/15/78.

He was re-admitted to the Mercy Hospital on 1/15/79 for re-evaluation. He had been asymptomatic since his previous discharge. Laboratory data showed a bilirubin of 2.2, alkaline phosphatase 182, SGOT 48. On 1/16/79, an ERCP demonstrated an enlarged opening from the previous sphincterotomy. The two stones remained in the common duct. On attempting to insert the papillotomy wire, it broke and the procedure was discontinued. He was discharged on 1/18/79. At his request, he was to return if he became symptomatic.

Discussion

The morbidity and mortality of biliary tract surgery rises with the age of the patient and the necessity to open the common duct. Moreover, many elderly patients have other serious medical problems, i.e., arteriosclerotic heart disease, COPD, cerebral and carotid vascular disease, and liver disease. The technique of endoscopic diagnosis and removal of common duct stones has been well developed in Germany. An ERCP is performed first. If common duct

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Fig. 1. Papillotomy wire in cutting position.



Fig. 2. Large arrow shows papillotomy wire in common duct in cutting position. Small arrows show two stones in the common duct.

stones are found, a catheter with a wire is then inserted through the sphincter of Oddi into the common duct. Radiofrequency current is passed along the wire as it is removed. This results in cauterization and cutting of the sphincter muscle and enlarging the opening. The common duct stones then pass into the duodenum. In the event they do not pass, the enlarged opening allows free passage of bile and prevents ascending cholangitis. Extensive experience in Germany[2,3,4] and limited experience in the USA[5] has shown a morbidity of 7% and mortality of 1.8%. These figures are similar to those obtained by surgery. However, 91% of patients with no complications have a 2 to 3 day hospitalization vs. a 10 to 14 day surgical hospitalization. These figures suggest that the procedure of choice is ERP with laparotomy reserved for complications and failures. My experience at the Mercy Hospital is limited, but it has demonstrated ease and safety of ERP by an experienced endoscopist.

Conclusion

The Mercy Hospital Gastrointestinal Service preliminary experience with ERP has shown it to be an easy, safe procedure when performed by an endoscopist experienced in ERCP. The failure of common duct stones to pass following papillotomy has not proved to be a "clinical" failure. The ampullary opening has been enlarged sufficiently to relieve the obstruction. Common duct stones cause pain, but more importantly they cause ascending cholangitis and obstructive jaundice. While pain may intermittently persist, prevention of jaundice and cholangitis may be sufficient in an elderly sick patient. This is especially so if the alternative is laparotomy and common duct exploration. In the future, there may be simpler techniques such as endoscopic retrograde chemical dissolution of common duct and gallbladder stones.

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Gallstone Ileus

Unusual Roentgenographic Manifestations of a Case

Douglas A. Howell, M.D.*

Abstract

A seventy-three-year old man developed a severe illness characterized by vomiting without abdominal pain, fever, and bacteremia. Serial roentgenograms after earlier UGI series showed evolution of a spontaneous cholecystoduodenal fistula and gallstone ileus. The clinical, pathologic and roentgenographic findings in this unusual illness are reviewed.

Introduction

Gallstone ileus is a mechanical bowel obstruction caused by a large gallstone impacting after entering the bowel lumen through a spontaneous cholecystoenteric fistula. Mortality of this illness is high and has been attributed to delay in diagnosis or occasionally an incorrect surgical procedure. Diagnosis is difficult since the triad of pneumobilia, calculus in the intestine, and a history of cholelithiasis is rarely present. Clinical findings can be highly variable and non-specific, making radiologic evaluation critically important. A recent case illustrates atypical clinical findings coupled with unusually illustrative roentgenograms.



Fig. 1. UGI series. Showing in retrospect barium coated radiolucent gallstone (↗) entering the duodenum through a cholecytoduodenal fistula. Pneumobilia is possibly present.

Case Report

A 73-year-old man was admitted in May 1978 to the Mercy Hospital for epigastric pain, elevated leukocytes but no fever. UGI series revealed a hiatal hernia and oral cholecystography showed a non-functioning GB as was seen 10 years earlier. He rapidly improved and was released. On Christmas Eve 1978, he developed nausea without pain and violent vomiting which lasted 24 hours. He had normal bowel movements, no chills or fever. His vomiting abated but nausea continued and after an additional four days he was admitted. On admission, he had no abdominal pain or distress except nausea, some hiccups and had had no stool for 72 hours. He denied a prior history of any major illness specifically ulcers, RUQ pains, or hospitalizations except a remote appendectomy.

Vital signs and examinations were normal, as were chest x-ray, CBC and SMA-12. Specifically, there were no abdominal findings.

Nausea and hiccups continued without vomiting. The morning after admission a temperature of 38.6 was noted and a scheduled UGI was done. Fig. 1 illustrates some confusing findings of a dilated stomach, a hiatal hernia with a possible ulcer, and in retrospect a large gallstone perforating into the duodenum.

Twenty-four hours later, his temperature rose to 39.4° and he became ashen and diaphoretic with rapid weak pulse and hypotension. Abdomen was silent but non-tender and leukocytes were 15,000 with 80% stabs with normal liver function tests. Repeat abdominal KUB (Fig. 2) showed free air under the left diaphragm. In retrospect, a strange barium coated defect was off the edge of the film and overlooked.

Emergency treatment for gram negative sepsis was begun to which he responded and repeat KUB was performed twelve hours later (Fig. 3). This study clearly showed a huge barium coated calculus obstructing the intestine which had shifted position. Pneumobilia was also present for the first time (Fig. 4). The diagnosis of gallstone ileus was made and emergency surgery removed a 4x6 cms. stone via a simple enterostomy (Fig. 5). The right upper quadrant was not explored. The patient recovered uneventfully.

Discussion

Gallstone ileus should always be considered as the cause for bowel obstruction in elderly patients especially if there is no history of prior abdominal surgery. The predominance of women beyond age 70 is noted in several series.[1,2] Some patients have the history of biliary colic but most do not. This suggests the fistula formation occurs by simple pressure necrosis by a large stone rather than cystic duct obstruction and gangrene. The adjacent viscus then becomes adherent and finally the fistula is formed. The duodenum is the most frequent site but sporatic cases involving the colon, stomach and even pleura and bronchus. Cholecystoenteric fistulas occur several times more frequently than gallstone ileus since the stone may pass without obstruction or remain in the gallbladder.[3,4] Twenty-five percent of fistulas are due to diseases other than cholelithiasis, mainly penetrating peptic ulcer disease and biliary, gastric or pancreatic cancer.

The point of obstruction generally occurs at the ileocecal valve, although rare cases document impaction in an area of narrowing in the sigmoid colon[5,6] or at the anus. The level of the obstruction may

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Fig. 2. Upright abdominal x-ray showing free air under left diaphragm (↗).



Fig. 3. Abdominal KUB with huge barium coated gallstone in the small intestine.



Fig. 4. Abdominal KUB confirming pneumobilia (↗).



Fig. 5. Huge radiolucent cholesterol gallstone removed at surgery. Actually, approximately the total size of a normal gallbladder.

descend producing brief episodes of spontaneous and misleading improvement. In general, the stone is larger than 2.5 cm and is radiolucent.

Since patients often present with obstruction which may occur days to months after asymptomatic passage of the stone into the gut lumen, an acute febrile illness such as our patient experienced is unusual. Bacteremia generally occurs only with evidence of ascending cholangitis, a complication common only with cholecytocolonic perforation. Free peritoneal air must be very rare since this finding is not mentioned in recent series. These unusual clinical features and the unique radiographic documentation of an evolving cholecystoduodenal fistula suggests acute gangrenous perforation occurred as opposed to the more frequent insidious formation mentioned above.

The diagnosis should be suspected on clinical grounds since radiographs may be non-specific. Air in the biliary tree is generally present but often overshadowed by dramatic changes of intestinal obstruction and overlooked. A radiopaque stone obstructing the intestine on plain roentgenograms is much less frequently seen. Barium, coating a radiolucent stone in our case, was both fortuitous and possibly unique.

If gallstone ileus is suspected but non-specific radiographs are obtained, an upper gastrointestinal series should be performed since the fistula often fills. A subsequent barium enema will be helpful if colonic perforation has occurred.[6]

Accurate diagnosis greatly simplifies the required emergency surgical approach which must be directed at removal of the obstructing stone. Occasionally a decompressing enterostomy must serve as the primary procedure.[6] A careful search for a second stone may avoid a prompt postoperative recurrence.

Right upper quadrant exploration is fraught with hazard in these very ill elderly patients and generally not indicated. Some authors reserve later cholecystectomy for those patients having recurrent gallbladder symptoms, a finding in less than 50% of patients.[7] Since in most patients a large solitary stone produced the ileus, recurrent intestinal obstruction rarely occurs and the fistula often heals.

Acknowledgement

I wish to thank Doctors Walter Goldfarb and Payson Adams who assisted in the evaluation of this complex patient.

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E R C P: The First 100 Cases—*Continued from Page 233*

dominal pain, fever, and elevated amylase. The patient recovered quickly with conservative medical therapy. In the second 50, there were no complications. One patient had pancreatitis and a cyst confirmed by ERCP. His pancreatitis was no more severe following the procedure. He recovered with medical treatment and hyperalimentation.

Conclusion

ERCP is a simple procedure easily and safely performed in a community hospital by a skilled endoscopist. The equipment needed is relatively inexpensive. This physician's experience of the first 100 cases in Maine agrees with the findings of others.[3,4]

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Psittacosis

William A. Demicco, M.D. and Dermot N. Killian, M.D., MRCP, FRCP (C)*

Psittacosis is an uncommon but potentially fatal infectious disease with mortality rates reported to range from 5-40%. The usual presentation is similar to atypical or viral pneumonitis except in that there is often a protracted high fever. Exposure to birds (parakeets, parrots, pigeons, turkeys most commonly) is usually the only medical clue leading to the appropriate diagnosis and antibiotic therapy.

The majority of cases in the United States, according to a 1974 study,[1] occur among the employees of turkey-processing plants. However, there is a smaller number of sporadic cases occurring in the United States among bird owners, dealers, and other persons exposed to birds. These cases continue to occur despite the availability of effective quarantine procedures which could eliminate this hazard.

We have recently encountered just such a case of sporadic psittacosis in Maine.

Case Report

Mr. R.W. is a 52-year-old male admitted to Mercy Hospital with a fever of 39.3° centigrade. He was in excellent health up until 72 hours prior to hospital admission when he experienced the onset of severe headache, profound weakness, and fever. At the time of admission he had no complaints of cough, other respiratory symptoms, abdominal pain, dysuria, or other localizing symptoms. However, careful history revealed that the patient was employed in a pet store and, in fact, routinely came into contact with sick or dead birds of various species.

Admission examination revealed a slightly dehydrated white male who nevertheless appeared healthy. Patient was febrile to 39.3° centigrade. Examination of the skin revealed no rash or petechia. Patient had no evidence of splinter hemorrhages or conjunctival hemorrhages. Patient's retinal examination revealed no lesions. Patient had no jaundice. Patient's oral muccosa was also free of lesions. Patient had no lymphadenopathy. Patient's chest was clear to auscultation and percussion. Patient had normal heart sounds without murmurs. Patient's abdomen revealed no enlargement of the spleen or liver or other masses. Patient's central nervous system examination was also totally normal, and there was no evidence of nuchal rigidity.

Patient's admission chest x-ray was entirely clear of infiltrates. Patient's admission white blood count was 8,500 cells/mm.^{3} Patient had blood, sputum, and urine cultures obtained, and he also underwent lumbar puncture which revealed clear spinal fluid with no red or white blood cells and normal protein and glucose. Culture of the spinal fluid was also sterile. Patient was begun on Oxicillin and Gentamycin. However, patient remained febrile with temperatures as high as 40° centigrade throughout the first six days of his hospitalization. All of his routine cultures failed to reveal any significant organisms. On the fourth hospital day, hematuria was noted along with the onset of a cough productive of small amounts of blood-tinged mucous. Chest x-ray still showed no infiltrate. On the fifth hospital day, rales were detected in the right lower lobe, and a repeat chest x-ray showed an infiltrate was now present in the right lower lobe distribution. After the pneumonitis developed, initial antibiotics were discontinued, and Erythromycin and Tetracycline begun orally.

Patient's temperature fell to normal within 48 hours, and a marked clearing of the chest x-ray was noted.

During the course of the patient's hospitalization, numerous laboratory tests were undertaken to determine the etiology of his illness. Among the negative serologic examinations were monospot test, hepatitis B surface antigen, febrile agglutinins, serum fungal titers, antinuclear antibody, and rheumatoid factor. Patient also had negative skin tests to intermediate strength PPD.

It was only after the patient recovered and returned home that the acute and convalescent antibody titers confirmed the clinical suspicion of psittacosis. Patient's antibody titers to chlamydia-psittacosis antigen showed a dilutional rise from a titer of 8 to 512 over a two week interval.

Discussion

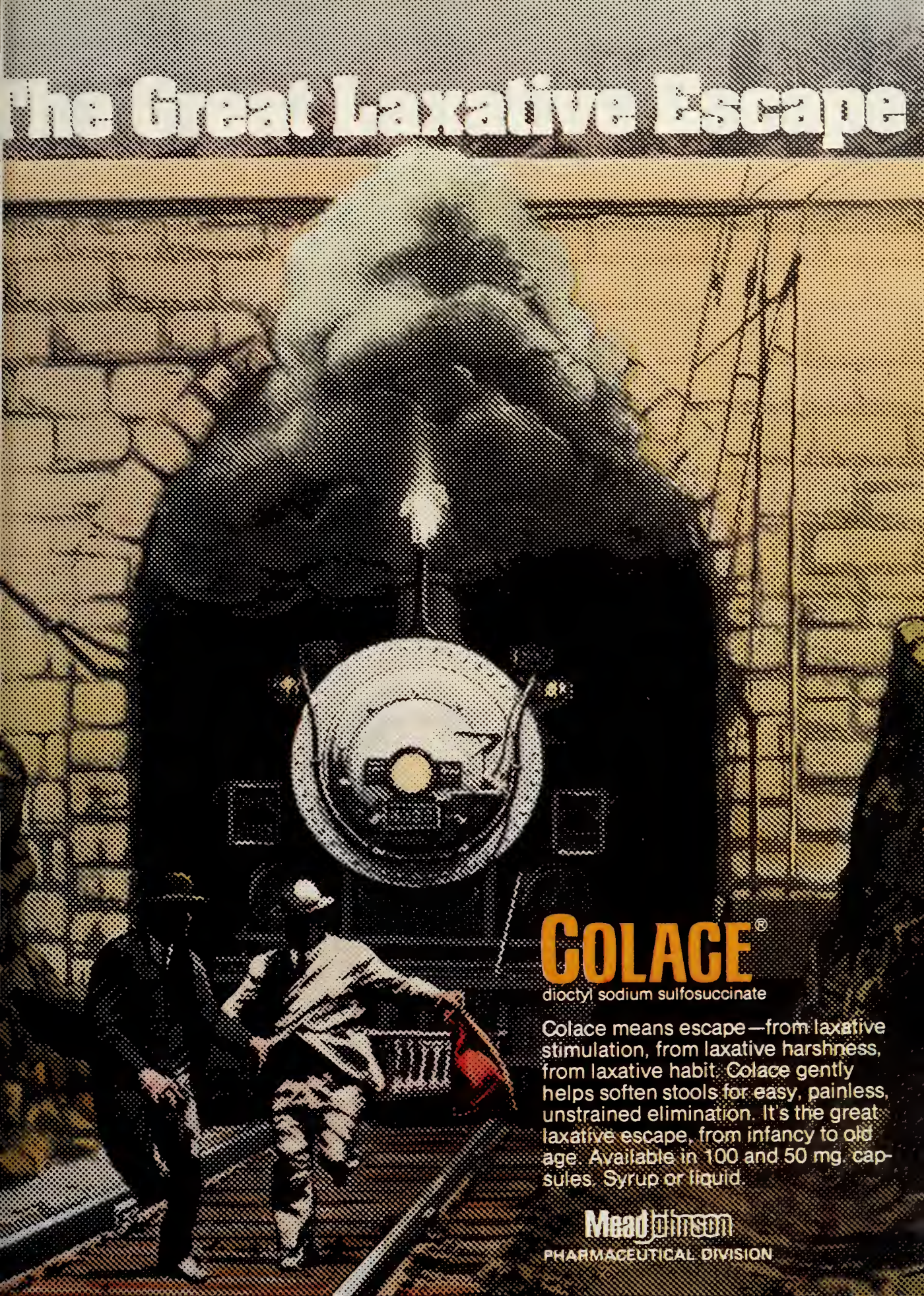
Patient's presentation is in many ways typical of the usual clinical picture of psittacosis. The illness often begins with a fever which persists for the first week of illness. Headache is often severe as it was in this case. Malaise is a common feature. Pneumonia is the most common organ involvement, but its presentation can be delayed until late in the first week of the illness as it was in this case. Even then, the physical findings of pneumonia may be minimal although the cough usually is productive of blood-streaked mucoid sputum, as was also the case with our patient. Other signs and symptoms which can be seen are myalgias, delirium and stupor, epistaxis, a macular rash, mild hepatomegaly and splenomegaly, jaundice, and, rarely, evidence of pericarditis, myocarditis, or pleuritis.

The specific diagnosis is usually made by serologic study with a four-fold rise in compliment fixating antibody titer being considered diagnostic. However, the treatment must usually be begun before confirmation of the disease. The Tetracycline is the drug of choice. Psittacosis (more properly called Ornithosis because it is not limited to parrots) is a chlamydial infection which humans contract from infected birds. However, the birds need not themselves be sick. The infective organisms are transmitted by parakeets (budgerigars), parrots, pigeons, turkeys, and cockatiels. In a review of psittacosis in the United States in 1974, compiled by the Center for Disease Control,[1] there were 163 cases of psittacosis reported. One hundred and seventeen of these cases occurred among employees of turkey-processing plants. The remaining 46 cases were sporadic infection, and in 37 of these 46 cases exposure to birds could be identified. The majority of cases were among pet bird owners.

Because pet birds usually of the psittacine species are the usual carriers of sporadic psittacosis infection, a system of quarantine for all incoming birds has been established by the U.S. Public Health Service. Presently birds are held for 30 days. Parakeets are treated with Chlorotetracycline—impregnated millet seeds, parrots with medicated mash, and other

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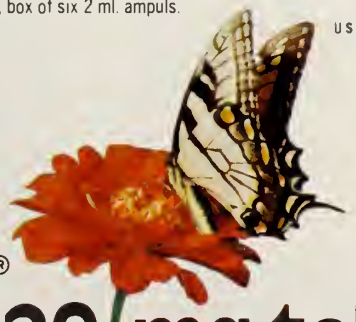
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Warnings: Do not administer more frequently than every 6 hours, or within 12 hours after rectal dose of any preparation containing theophylline or aminophylline. Do not give other compounds containing xanthine derivatives concurrently

Precautions: Use with caution in patients with cardiac disease, hepatic or renal impairment. Concurrent administration with certain antibiotics, i.e., clindamycin, erythromycin, troleandomycin, may result in higher serum levels of theophylline. Plasma prothrombin and factor V may increase, but any clinical effect is likely to be small. Metabolites of guaifenesin may contribute to increased urinary 5-hydroxyindoleacetic acid readings, when determined with nitrosonaphthol reagent. Safe use in pregnancy has not been established. Use in case of pregnancy only when clearly needed

Adverse Reactions: Theophylline may exert some stimulating effect on the central nervous system. Its administration may cause local irritation of the gastric mucosa, with possible gastric discomfort, nausea, and vomiting. The frequency of adverse reactions is related to the serum theophylline level and is not usually a problem at serum theophylline levels below 20 mcg/ml.

How Supplied: Capsules in bottles of 100 and 1000 and unit-dose packs of 100; Liquid in bottles of 1 pint and 1 gallon.

See package insert for complete prescribing information.

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Where There's A Will There's A Way

John P. Dow, M.D.*

Shortly after World War II, a small, nameless country, relatively untouched by the war, and blessed with an energetic and far sighted people, achieved a stunning success. Recovering from years of oppressive rule, the citizens embraced the tenets of democracy and laissez faire. Their experience as suppliers of aircraft parts for the war and their natural drive, led them to launch the commercial aircraft industry.

Over the ensuing years, they developed the largest, most efficient, most technologically advanced aircraft in the world. They were, in short, the biggest and the best, the envy of the modern world.

Arising with the industry was a corps of professional pilots, whose life work and enduring pride was to be the captains of these ships. The lives of countless passengers rode with the skilled hands and minds of these professionals.

As the demands upon the profession rose, so did the time and effort required to master it. The dream of many young boys and girls in the country was to rise to this pinnacle of professional excellence. It was obvious that the economy and the society could not train them all, and only the very best made it. Accordingly, as in any free society, their rewards were commensurate with their advanced training and professional responsibility.

Years passed. The world changed. Everyone was flying everywhere, placing ever increasing demands upon the profession. The machines became so complex that enormous support facilities and personnel were required to maintain and operate the system. The pilots soon had little time to ground check their aircraft, or to chat with passengers, or to navigate, or to monitor the engines, and so on...

Soon wholly new disciplines grew up, merely to support the pilot and his craft. The entire society was obsessed with flying. No one was obsessed with navigation, maintenance schedules, operations, or passenger feeding, especially not the pilots.

The pilots had almost forgotten how to do these mundane chores, but the ground crew had discovered that flying, a single engine, fabric covered airplane, was not so difficult and took only several weeks to learn. Now the ground crew could "fly" *and* maintain the aircraft.

Unions evolved among the support personnel. Soon the ground crew demanded a representative in the cockpit. Why not, the pilot was still in command? Shortly thereafter, the harassed, fatigued, individualistic and very unorganized pilots allowed, under union pressure, the crewmen to fly, at very high altitudes and under very safe conditions.

Meanwhile, back in the passenger section, the stewardesses were taking crash courses in flying. Why not, it worked for the ground crew and that was where the action was?

Pilots soon found that they had only time for takeoffs and landings.

More years passed, the pilot was still comfortable in a much smaller seat and the cockpit had expanded to include a fair amount of passenger and cargo space in order to accommodate the large crew. Costs obviously soared, and the very democratic government, under the pressing needs of the economy, decided to apply the pinch.

Eventually it occurred to a narrow little aide of a very big man that the pilot's presence might not be required at all. By now his crew was licensed in the various operations of flying, and the marvelous technology did all the rest.

This idea was studied thoroughly by a committee of passengers and stockholders in the airline industry, and the idea was unique. The pilots would be made "managers" of the flight crew and would be given a large desk in an impressive building. After all, this was the pinnacle of control. The desk soon became buried in xeroxed copies of maintenance schedules, accident reports, and mental fatigue and stress statistic reports. Papers spilled, untouched and unseen, into the shredder.

More time passed.

Only last week a clerk typist from operations made a shaky but costless landing after a 10 day flight course. Efficiency was paying off. The old barnstorming motto of "any landing you walk away from is a good one" was painted on the file cabinet door. The clerk typists have now petitioned the legislature to be a part of the flight crew and have suggested that a new profession of assistant clerk typist be created to help the pilot-manager in his office. All will be licensed if the bill passes.

The planes still fly and the end of the story is near—but not yet written.

*Chairman, M.M.A. Legislative Committee.

From the Secretary's Notebook

Summary of Proceedings, Interim Meeting, M.M.A. House of Delegates, April 7, 1979 in Waterville, Maine

The Interim Meeting of the M.M.A. House of Delegates was held at the Mid-Maine Medical Center in Waterville on Saturday, April 7, 1979 with an attendance of 64 delegates and alternates and 6 guests. Francis I. Kittredge, M.D., President of the M.M.A., called the meeting to order and George W. Bostwick, M.D., Speaker of the House, presided.

1. **Reports of Officers**—Dr. Kittredge spoke regarding Senate Bill 505.

2. **Financial Statement of Income and Expenditures for 1978 and Budget Proposed for 1980,** was presented by Dr. Richard Leck, Chairman of the Budget Committee. He pointed out that the large deficit was, for the most part, because of the estimated expenses of a new building, and expected that new figures would be hammered out between now and June. Final action on the proposed budget for 1980 will take place at the annual meeting of the House of Delegates on June 16 and 17, 1979 at the Samoset Resort Inn in Rockport.

3. The preliminary report of the **Committee on Nominations** (printed) was given to each delegate. The report consisted of nominees for vacancies on the standing committees, for President-elect, AMA Delegate and Alternate, and for each position to be filled on the Executive Committee (this year, Districts 1, 5 and 6). **A brief biographical sketch of each officer nominee** was sent to members of the House of Delegates. Nominees for any officer position may be made from the floor.

4. **Committee Reports:**

a) *Building*—Dr. John Wickenden, Chairman, recalled that at the last meeting of the House of Delegates, they were instructed to go ahead with the building, with a total cost of around $250,000. Plans came in at $275,000 (without solarium, landscaping and extra insulation which would add an additional $38,919). Cost of land and architect fees would bring the project cost to $330,000. Architect William Sepe briefly outlined the building plans.

b) *Building Finance Committee*—Dr. Thomas Feagin, Chairman, presented three options to the delegates for consideration:

Option A = New Building as presented, with solarium (does not include cost of land, architect fees or escalation)

Option B = New Building, reduced size of structure (remove conference room and solarium), with material and equipment substitutions (does not include cost of land, architect fees or escalation)

Option C = Purchasing existing building at cost of up to $80,000 and sell lot at Civic Center Complex

After considerable discussion, it was "moved that the M.M.A. dispense with the concept of a new building and adopt Option C (buy and renovate house in Augusta) and sell the lot. Further, that the possibility of a future building not be precluded." The motion was *carried*, 35 to 21.

Dr. Wickenden and his committee were thanked for their efforts to date.

OPTION A	*OPTION B*	*OPTION C*
$315,000	$225,000	$80,000
$100 Assessment = $105,000	$100 = $105,000	−35,000 — lot
		$45,000
$210,000 Mortgage	$120,000 Mortgage	Mortgage
$25-28,000 Debt Service	$12,000 Debt Service	$4,500 Debt Service
$21,000 Operating Expenses	$14,000 Operating Expenses	$7,500 Operating Expenses
$46/member/year @ 1,000 members	$26/member/year @ 1,000 members	$12/member/year @ 1,000 members
+$100 Assessment	= $100 Assessment	= $0

5. **Resolutions** — Four resolutions were presented to the delegates (copies sent to all delegates on 4/2/79), and all will be referred to the June 1979 meeting of the House of Delegates for action.

6. Dr. Bostwick announced members who will serve on **Reference Committees** during the Annual Meeting in June.

7. Other —

a) Dr. John Zerner reported on L.D. 635, a bill sponsored by Rep. Merle Nelson, entitled "An Act Concerning Persons Exposed to Diethylstilbestrol." He asked that physicians provide support by helping to inform patients and sensitize them to the need for a checkup. He also asked help in informing the practicing physicians in Maine of the **DES** situation in exposed females, and to suggest that a continuing program of education and evaluation, such as that broadly suggested by L.D. 635, be supported.

b) Mr. Stred appealed to the delegates for help in **legislative matters**, and alerted them to the fact that he might be calling on them individually for assistance.

8. Adjourned at 4:30 P.M.

PATRICIA A. BERGERON
Secretary-Treasurer

PSITTACOSIS—*Continued from Page 240*

antibiotic prophylaxis for other incoming birds. Nevertheless, from a study from San Francisco, California,[2] where 101 parakeets and pigeons were examined, *Chlamydia psittaci* were recovered from 34% of the parakeets and 40% of the parrots tested. Although these birds were examined because of death, sickness, or suspicion of exposure to other sick birds, the results, nevertheless, point out the persistent reservoir of psittacosis in this country. Many of these birds had, in fact, been recently imported and could be traced back to quarantine centers where, supposedly, they had been prophylactically treated for Chlamydial infection. The conclusion of this report was that the quarantine procedures, at least in California for the years 1975-1976, were inadequate. Psittacosis infection persists as a potentially fatal infection in the United States and must be considered in any febrile patient with pneumonic disease for which other diagnosis is not established.

REFERENCES

1. Durfee, P.: "Psittacosis in Humans in the United States, 1974;" *J. Inf. Dis. 132:* 604 1975.
2. Schachter, J., Sugg, N., and Sung, M.: "Psittacosis: The Reservoir Persists;" *J. Inf. Dis. 137:* 44 1978.
3. Schaffner, W., Prutz, D.J., and Koenig, M.G.: "The Clinical Spectrum of Endemic Psittacosis;" *Arch. Intern. Med. 119:* 433 1967.
4. Rogers, D.E.: "Psittacosis in Beeson, P.B. and McDermott, W. (editors) Textbook of Medicine;" W.B. Saunders Co., Philadelphia 1975.

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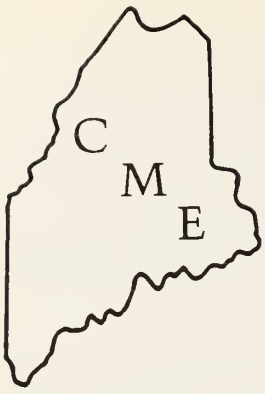
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CONTINUING MEDICAL EDUCATION IN MAINE

Conferences and Workshops

Title: **The Raymond P. Sloan Institute on Health Care Policy and Management**
Date: June 27-29, 1979
Location: Colby College
Sponsors: Colby College and Maine Hospital Association
Credit: AMA Category I—12 hours
Reg. Fee: $135.00 (reduction if single organization sends more than two representatives)
For further information contact Robert H. Kany, Ph.D.; 873-1131

Title: **Sports Medicine Seminar**
Date: June 27-30, 1979
Location: Bowdoin College, Brunswick
Sponsors: Bowdoin College; Regional Memorial Hospital; Medical Care Development, Inc.
Credit: AMA Category I—19 hours
Reg. Fee: $220.00
For further information contact Joanne C. LeBlanc; 729-0181

Title: **Management Systems for Hospital Cost Containment**
Date: August 16-18, 1979
Location: Shawmut Inn; Kennebunkport
Sponsors: Maine Hospital Association; Maine Voluntary Cost Containment Committee
For further information contact Margery Read; 622-4794

Title: **Family Medicine—Update**
Date: September 24-26, 1979
Location: Samoset Resort Inn, Rockport
Sponsor: Medical Care Development, Inc.
Credit: AMA Category I—15 hours; AAFP (prescribed)—15 hours
Reg. Fee: $150.00
For further information contact Gerald Goold; 622-7566

Programs Sponsored by Mid-Maine Medical Center/Colby College

Title: **Allergy and Immunology**
Date: July 2-5, 1979
Location: Colby College
Credit: AMA Category I—16 hours; AAFP (elective)—16 hours
Reg. Fee: $250.00

Title: **Topics in Emergency Medicine**
Date: July 8-12, 1979
Location: Dean Auditorium, Mid-Maine Medical Center (MMMC)
Credit: AMA Category I—22 hours; AAFP (prescribed)—22 hours
Reg. Fee: $275.00

Title: **Epilepsy Seminar**
Date: July 10-14, 1979
Location: Colby College
Credit: AMA Category I—19 hours; AAFP (elective)—19 hours
Reg. Fee: $235.00

Title: **Topics in Pediatrics**
Date: July 15-19, 1979
Location: Colby College
Credit: AMA Category I—17 hours; AAFP (elective)—17 hours
Reg. Fee: $210.00

Title: **Surgical Techniques and Problems**
Date: July 17-20, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—15 hours
Reg. Fee: $185.00

Title: **Hematology—Disorders of Maturation and Proliferation**
Date: July 22-26, 1979
Location: Colby College
Credit: AMA Category I—18 hours
Reg. Fee: $225.00

Title: **Neurosurgical Techniques**
Date: July 22-26, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—21 hours
Reg. Fee: $260.00

Title: **Office Dermatology**
Date: July 29-August 2, 1979
Location: Colby College
Credit: AMA Category I—16 hours; AAFP (prescribed)—16 hours
Reg. Fee: $200.00

Title: **F. T. Hill Seminar in Otolarngology**
Date: July 29-August 2, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—18 hours
Reg. Fee: $225.00

Title: **Ophthalmology Seminar**
Date: August 5-9, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—18 hours
Reg. Fee: $225.00

Title: **Topics in Clinical Nuclear Medicine**
Date: August 12-17, 1979
Location: Colby College
Credit: AMA Category I—30 hours
Reg. Fee: $350.00

Title: **Current Aspects of Obstetrics and Gynecology**
Date: August 12-16, 1979
Location: Colby College
Credit: AMA Category I—18 hours; AAFP (elective)—18 hours
Reg. Fee: $225.00

Title: **Continuing Topics in Forensic Sciences**
Date: August 19-23, 1979
Location: Colby College

Credit: AMA Category I—21 hours; AAFP (elective)—21 hours
Reg. Fee: $275.00

Title: **Topics in Pulmonary Disease**
Date: August 19-23, 1979
Location: Colby College
Credit: AMA Category I—19 hours
Reg. Fee: $240.00

For further information on all the programs sponsored by Mid-Maine Medical Center/Colby College, contact Robert H. Kany, Ph.D.; Division of Special Programs, Colby College; Waterville, Maine 04901; 873-1131

Hospital Activities

Augusta General Hospital
Augusta, Maine

June 26, 1979 — **Dermatology Conference**
7:30-8:30 a.m. — Daniel Clarke, M.D., Augusta General Hospital

July 24, 1979 — **Endocrine Conference**
7:30-8:30 a.m. — Hugh Johnston, M.D., Thomas Bigos, M.D., or Richard Eastman, M.D., Maine Medical Center

Programs have been certified AMA Category I and AAFP (prescribed). For further information contact Mrs. Nancy York; 623-4711. Programs may be viewed over ITS.

Dean Hospital
Greenville, Maine

July 20, 1979 — **Clinical Consultations—Cardiovascular Disease**
9:30 a.m.-Noon — Larry Nolin, M.D., MMMC

August 17, 1979 — **Clinical Consultations—Oncology**
9:30 a.m.-Noon — Eugene Beaupre, M.D., MMMC

Eastern Maine Medical Center
Bangor, Maine

Every Mon.	EEG Conference	12-1 p.m.
Every Mon.	Surgical Service—Chief's Rounds	5-6 p.m.
4th Mon.	ENT Section Meeting	12-1 p.m.
4th Mon.	Neurosurgery Section Meetings	4-5 p.m.
3rd Tues.	Dermatology-Pathology Conference	5-6 p.m.
3rd Tues.	Dermatology Section Meeting	6-7 p.m.
4th Tues.	Pulmonary Medicine Section Meeting	8-9 a.m.
1st Wed.	Hematology/Oncology Meeting	8-9 a.m.
Every Wed.	Tumor Clinic Conference	2-5 p.m.
Every Wed.	Radiology Conference (1) Ultrasound/Nuclear Medicine (2) Radiology Film Review (3) Neuroradiology (4) Teaching File Conference	5-6 p.m.
1st Thurs.	Ophthalmology Section Meeting	7:30-8:30 a.m.
	OB-GYN Conference (1) Pathology (2) GYN Analysis (3) OB-Pediatric Combined (4) In-Service and Education	8-9 a.m.
Every Thurs.	Pediatric Grand Rounds	9-10 a.m.
Every Thurs.	Medical Service Conference	10-11 a.m.
Every Thurs.	Cardiology Conference	11a.m.-1 p.m.
2nd Thurs.	Orthopedic Grand Rounds	7:45-8:45 a.m.
4th Thurs.	Orthopedic Service Meeting	7:30-9 a.m.
4th Thurs.	Surgical Service Death Review	7:45-8:45 a.m.
Every Thurs.	Psychiatric Service Grand Rounds	10-11 a.m.
4th Thurs.	Urology Section Conference	7:30-8:30 a.m.
Every Fri.	Neurology Grand Rounds	8-9 a.m.

Visiting Professor Program:

2nd Thurs.	Medical Service Visiting Professor	10 a.m.-5 p.m.
2nd Thurs.	Anesthesia Service Visiting Professor	7-8 a.m.
3rd Thurs.	OB/GYN Service Visiting Professor	10 a.m.-4 p.m.
Saturdays	Surgery Service Visiting Professor	8 a.m.-Noon
4th Thurs.	Pediatric Service Visiting Professor	10 a.m.-5 p.m.
as scheduled	Orthopedic Service Visiting Professor	
as scheduled	Family Practice Visiting Professor	
as scheduled	Psychiatric Service Visiting Professor	
as scheduled	Radiology Service Visiting Professor	

All activities have been certified AMA Category I. For further information contact Robert H. Brown, M.D., Chairman, Med. Ed. Committee; 947-3711 Ext. 330.

Franklin County Hospital
Farmington, Maine

July 2, 1979 — **Immunology-Allergy Conference**
6-8:30 p.m. — Robert Sylvester, M.D., CMMC, and Geoffrey Gratwick, M.D., EMMC

All activities have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621.

Mid-Maine Medical Center
Waterville, Maine

June 28, 1979 — **Perinatology**
David Nochimson, M.D., Baystate Medical Center, Springfield, Mass.

July 5, 1979 — **Rheumatology Series—Ankylosing Spondylitis and HLA Antigens**
Currier McEwen, M.D., Regional Memorial Hospital

July 12, 1979 — **Psychiatry**
Ronald Abramson, M.D., Tufts University School of Medicine

July 19, 1979 — **Electrolyte Series—Hyponatremia**
Don Leeber, M.D., Maine Medical Center

July 26, 1979 — **Rheumatology Series—Non-Articular Rheumatism**
Currier McEwen, M.D., Regional Memorial Hospital

All programs run from 12-1 p.m. and have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621. Programs may be viewed over ITS.

Redington Fairview Hospital
Skowhegan, Maine

June 27, 1979 — **Endocrinology Conference**
12-1 p.m. — Richard Eastman, M.D., Maine Medical Center

July 25, 1979 — **Rheumatology Conference**
12-1 p.m. — Sidney Block, M.D., Eastern Maine Medical Center, and Currier McEwen, M.D., Regional Memorial Hospital.

All activities have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621.

NEW TEL-MED TAPES AVAILABLE

There are now fifty-six new tapes available through Tel-Med, Blue Cross and Blue Shield of Maine's dial-in health information system (listed below). Maine people can hear health information tapes on subjects ranging from warning signals of cancer to bee stings.

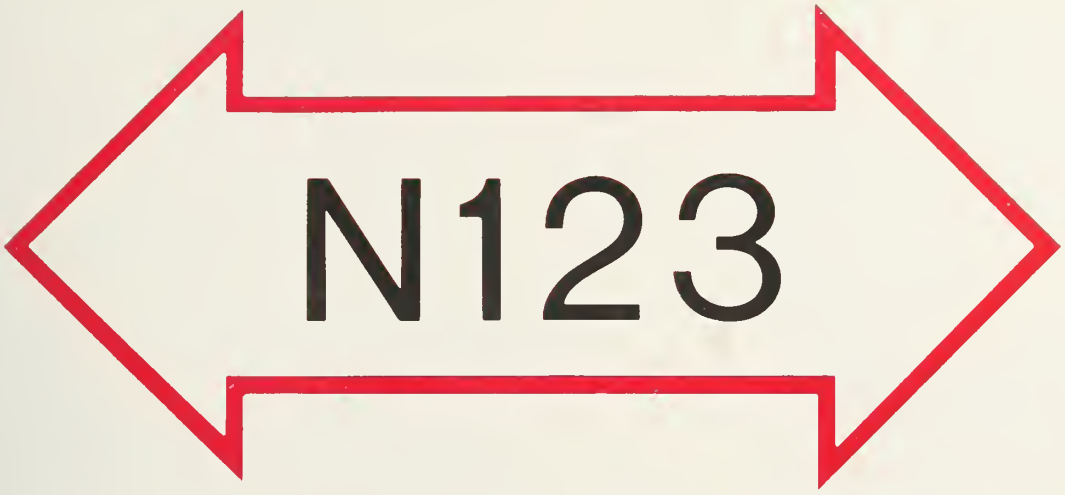
16. Gonorrhea
67. Warning Signs in Pregnancy
4. Hemorrhoids
96. Poisoning by Mouth
180. Cancer of Colon and Rectum
239. Innoculations for Children
54. Birth Control
10. Poisons in the Home
943. Is Drinking a Problem?
945. So You Love An Alcoholic?
944. To Drink or Not To Drink
79. Dandruff
130. Drug Abuse Resources
32. Unwanted Pregnancy
24. Abortion
48. Thumb Sucking
56. Intrauterine Devices
66. Miscarriages
12. Am I Pregnant?
49. No-No To The Toddler
47. Leg Cramps & Aches
57. The Rhythm Method
42. I'm Just Tired Doctor
50. Teen Years—Age of Rebellion
17. Lockjaw
172. Acne
137. Marijuana
700. Effects of Cigarette Smoke on Non-Smokers
15. Syphilis
77. Kidney Stones
121. Bee Stings
63. Early Warning of Heart Attack
565. Hypoglycemia
970. Herpes
263. Teething
194. Slipped Disc
183. Cancer—Seven Warning Signals
166. Medical Supplies for the Home
150. Seat Belts
400. Tommy Gets His Tonsils Out
604. A Guide to Good Eating
309. Canker Sores and Fever Blisters
138. Narcotics
133. Advice for Parents of Teenagers
83. Impetigo
52. Lice—Pubic, Head and Body
229. Chickenpox
185. Cancer of the Skin
175. Fears of After Forty Man
162. Hepatitis
29. Atherosclerosis & High Blood Pressure
147. Lady Living Alone
136. Amphetamines & Barbiturates
127. Arthritis—Rheumatism
148. Muggings & Purse Snatching
30. Angina Pectoris

Tel-Med, first introduced in 1976, is a collection of tape recorded health messages developed with the cooperation of the Cumberland County Medical Society, the Maine Medical Association and the Maine Osteopathic Association. The tapes are 3 to 7 minutes in length, and are narrated in easy-to-understand language.

The Tel-Med system is designed to provide people with preventive health information; to help them recognize early signs of illness; or to help them adjust to a serious illness. Since its start, Tel-Med has logged well over 45,000 calls.

Public response to Tel-Med has been quite good, and many physicians, hospitals, counseling centers and other community service organizations have referred others to the Tel-Med tape library.

Free brochures listing all 123 Tel-Med tapes are available by writing to Tel-Med, c/o Blue Cross and Blue Shield of Maine, 110 Free Street, Portland, Maine 04101.



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News, Notes and Announcements

Maine Society for the History of Medicine

A meeting of physicians interested in forming a MAINE SOCIETY FOR THE HISTORY OF MEDICINE is planned for Saturday, September 15, 1979 at 2:00 P.M. in the Conference Room of the Physicians Office Building, Penobscot Bay Medical Center, Rockland, Maine. A brief organizational meeting will be followed by a program of historical interest. You are invited to be present as a charter member of the society.

All those who plan to attend or are interested in membership are asked to contact:

Richard J. Kahn, M.D., F.A.C.P.
Pen Bay Physicians Building
Rockland, Maine 04841

State of Maine
Department of Human Services
Division of Child Health Clinic Schedule—1979

By Appointment Only

Orthopedic Clinics

Bangor—St. Joseph Hospital
9:00 a.m.: Mar. 22, Apr. 26, May 24, June 28, July 19, Aug. 23, Sept. 27, Oct. 25, Nov. 15, Dec. 20

Fort Kent—Northern Maine Medical Center
9:00 a.m.: Mar. 13, May 15, July 10, Sept. 11, Nov. 6

Houlton—Houlton Regional Hospital
10:00 a.m.: Mar. 12, May 14, July 9, Sept. 10, Nov. 5

Presque Isle—A.R. Gould Memorial Hospital
9:00 a.m.: Mar. 14, May 16, July 11, Sept. 12, Nov. 7

Waterville—Mid-Maine Medical Center (Seton Unit)
Time scheduled by hospital: Mar. 5, Apr. 2, May 7, June 4, Sept. 10, Oct. 1, Nov. 5, Dec. 3

Cleft Palate Clinic

Portland—Maine Medical Center
9:00 a.m.: May 21, June 18, Sept. 17, Oct. 15, Nov. 19

Cardiac Clinics

Bangor—St. Joseph Hospital
9:00 a.m.: Mar. 9, Apr. 13, May 11, June 8, July 13, Aug. 10, Sept. 14, Oct. 12, Nov. 9, Dec. 14

Portland—Maine Medical Center
9:00 a.m.: Mar. 2, 9, 16, 23, 30, Apr. 6, 13, 20, 27, May 4, 11, 18, 25, June 1, 8, 15, 22, 29, July 6, 13, 20, 27, Aug. 3, 10, 17, 24, 31, Sept. 7, 14, 21, 28, Oct. 5, 12, 19, 26, Nov. 2, 9, 16, 30, Dec. 7, 14, 21, 28

Children's Development Clinic

Lewiston—Central Maine Medical Center
8:30 a.m.: Mar. 12, Apr. 9, May 14, June 11, July 9, Aug. 13, Sept. 10, Nov. 26, Dec. 10

County Society Notes

Knox

The Knox County Medical Society met at the Sail Loft Restaurant in Rockport on January 9, 1979.

Twenty-one members were in attendance. Dr. Russell, a new physician in the area, was an invited guest.

Following the dinner, the meeting was called to order by the President, Dr. Barbara L. Fuller.

The nominating committee presented the slate of new officers for 1979:

President: Dr. Barbara L. Fuller, Rockland
Vice-President: Dr. Corwin A. Olds, Rockland
Secretary: Dr. Albert J. Lantinen, Glen Cove

Discussion then centered around proposal at the previous business meeting that the officers serve a two year term in office progressive to the next higher office. This would involve a new secretary/treasurer being nominated every two years. After discussion, a vote was taken and the rule change unanimously passed.

A slate of delegates to the Maine Medical Association was presented. Delegates will be Drs. David G. Reed, Camden, Peter R. Shrier, Glen Cove and Lloyd Roberts, Rockland. Alternate delegates will be Drs. Gordon T. Paine, Jr., Roger W. Wickenden and Edward K. Morse, all of Rockland.

Dr. Julian Sacks and Dr. Robert P. Laurence were presented for a vote on membership. Their credentials were in order. They were elected to membership unanimously.

The previous suggestion of Dr. John Williams that the method of collecting the cost of dinner at each meal be changed resulted in lively discussion on two proposals. Neither proposal gained acceptance and the matter was tabled.

Dr. Barbara Fuller read a letter from Kno/Wal/Lin Health Services asking for the Society's support to run a blood pressure screening clinic at various industrial locations within the three counties. They will be using the Chicago criteria of hypertension. The Society unanimously voted its approval of such an effort.

House of Delegates report: Dr. John Wickenden reported on the proposed new location of the Maine Medical Association in Augusta. He stated the land had been purchased and preliminary architectural drawings have been approved. Further meetings will be held in this regard. Dr. Peter Shrier reported on Blue Shield negotiations. The main points centered around the Service Benefit Clause and the reimbursement of nonparticipating physicians. It seems apparent that this discussion is at a stalemate and further input was requested from the members by Dr. Shrier.

Following the business meeting, Dr. Richard Kahn presented a discussion of the development of anatomy and related subjects, in particular acquisition of cadavers. This was highlighted by an excellent film from Yale University.

There being no further business, the meeting was adjourned at 9:45 p.m.

The Knox County Medical Society met at the Sail Loft Restaurant in Rockport on February 6, 1979. Thirty-one members were in attendance.

Following dinner, a short business meeting was held. Drs. Olaf Anderson and Judith Anderson were elected to membership in the Knox County Medical Society. Dr. Peter Shrier requested that all members reply to the questionnaire being sent out by the Committee on Health Care Financing. This questionnaire deals with members' feelings towards Blue Cross negotiations. He requested that members give careful consideration to the questionnaire.

Dr. Robert Wise, Medical Director of the Veterans Administration Hospital in Togus, then presented an extensive history of the discovery of Legionnaire's disease. Of interest is the fact that a Togus strain of this disease has been discovered.

There being no further business, the meeting was adjourned at 10:00 p.m.

The Knox County Medical Society met at the Sail Loft Restaurant in Rockport on March 6, 1979. Thirty-one members were in attendance. Invited guests were Dr. and Mrs. Francis Kittredge, Dr. Jeremy Morton, Dr. Dan Hanley and Dr. Richard Leck.

Following the dinner, the meeting was called to order by Dr. Barbara L. Fuller, President. Short discussion centered around the M.M.A. request for a copy of our bylaws. Only one copy is known to exist and a committee was formed to review these bylaws and

Continued on Page 250

In Edema* or Hypertension* when potassium balance is a concern...

Potassium-Sparing

DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Makes Sense

In Edema

The triamterene in 'Dyazide' limits potassium loss and provides an additive diuretic effect to that of the hydrochlorothiazide component.

In Hypertension

As the hydrochlorothiazide in 'Dyazide' lowers blood pressure, the triamterene component limits potassium loss.

Serum K^+ and BUN should be checked periodically particularly in the elderly, diabetics, and those with suspected or confirmed renal insufficiency (see Warnings). If hyperkalemia develops, substitute a thiazide alone.



Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in postsympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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Carolina, P.R. 00630

When painful spasm is the presenting symptom . . .



..in the functional bowel/irritable bowel syndrome*

Bentyl®

(dicyclomine hydrochloride USP)

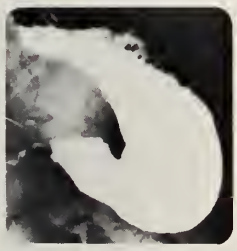
10 mg. capsules, 20 mg. tablets,
10 mg./5 ml. syrup, 10 mg./ml. injection

helps control abnormal motor activity
with minimal anticholinergic side effects†

Demonstrated smooth muscle relaxant activity.

In this double-blind study, twenty patients having G.I. series and exhibiting spasm were randomly selected to receive either 2 cc. of Bentyl or sodium chloride intramuscularly. Ten minutes after the injection another radiograph was taken . . .

. . . Bentyl produced definite relaxation in 8 of 10 patients. The sodium chloride produced relaxation in only 3 of 10. No side effects occurred in either group of patients.



Pylorospasm has almost totally blocked passage of barium meal.



Barium meal beginning to pass 10 minutes after intramuscular injection of 20 mg. Bentyl.

"The correlation of spasm relief and drug given was excellent."

*This drug has been classified 'probably' effective in treating functional bowel/irritable bowel syndrome

†See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964.

Merrell

8-4420 (Y736A1) MNR-804

Bentyl®

(dicyclomine hydrochloride USP)

Capsules, Tablets, Syrup, Injection

AVAILABLE ONLY ON PRESCRIPTION

Brief Summary

INDICATIONS

Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the following indications as "probably" effective:

For the treatment of functional bowel/irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

THESE FUNCTIONAL DISORDERS ARE OFTEN RELIEVED BY VARYING COMBINATIONS OF SEDATIVE, REASSURANCE, PHYSICIAN INTEREST, AMELIORATION OF ENVIRONMENTAL FACTORS.

For use in the treatment of infant colic (syrup).

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient; unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: Autonomic neuropathy. Hepatic or renal disease. Ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension. Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia; urinary hesitancy and retention; blurred vision and tachycardia; palpitations; mydriasis; cycloplegia; increased ocular tension; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs.

Usual Dosage: Bentyl 10 mg capsule and syrup: *Adults*: 1 or 2 capsules or teaspoonfuls syrup three or four times daily. *Children*: 1 capsule or teaspoonful syrup three or four times daily. *Infants*: ½ teaspoonful syrup three or four times daily. (May be diluted with equal volume of water.) Bentyl 20 mg: *Adults*: 1 tablet three or four times daily. Bentyl Injection: *Adults*: 2 ml. (20 mg.) every four to six hours intramuscularly only. NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE: The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

Product information as of October, 1978.

Injectable dosage forms manufactured by CONNAUGHT LABORATORIES, INC., Swiftwater, Pennsylvania 18370 or TAYLOR PHARMACAL COMPANY, Decatur, Illinois 62525 for MERRELL-NATIONAL LABORATORIES, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215, U.S.A.

Merrell

MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215, U.S.A.

present them at the next county meeting. Following this, with no further business, a discussion of current coronary bypass surgery experience at Maine Medical Center was presented by Dr. Jeremy Morton. Following this, discussion of Maine Mutual Insurance Company's progress in the field of liability insurance was presented by Drs. Hanley, Leck and Morton.

There being no further business, the meeting was adjourned at 10:00 p.m.

ALBERT J. LANTINEN, JR., M.D., *Secretary*

Oxford

A regular meeting of the Oxford County Medical Society was held on January 10, 1979 a The Bethel Inn, Bethel, with fifteen members, including one senior member, present.

The meeting was called to order by Dr. H. Richard Bean, President.

The reading of the previous minutes was dispensed with.

Drs. Charles M. Smith, James C. Delehanty and Linda K. Tyer were unanimously elected to membership.

Dr. Bean introduced Dr. Charles M. Smith, Orthopedic Surgeon, who presented a Scientific Session on "Surgical Treatment of Arthritis." Dr. Smith presented interesting clinical and radiological findings in arthritic patients and discussed the surgical treatment, as well. His presentation was followed by questions and answers on the subject.

The Society directed the secretary to invite Dr. George N. McNeil, Department of Psychiatry, Maine Medical Center, Portland, to discuss psychiatric problems and related management at a future meeting. At the same time, the Society declined to schedule a time for representatives from Blue Cross-Blue Shield of Maine for purpose of presentation of "The Blue Shield Story."

Society members voted to change the meeting months of April and June to March and May, in order that the latter two months do not conflict with the Annual Meeting of the Maine Medical Association in June.

The Society unanimously nominated Dr. Paul A. Brinkman, Farmington, as District Councillor, and recommended his name to the Maine Medical Association.

The Secretary-Treasurer informed the members that the current account balance is $362.13.

Members then adjourned for dinner which was enjoyed by all.

HARBANS S. SODHI, M.D., *Secretary*

Penobscot

The January meeting of the Penobscot County Medical Society was held on January 16, 1979 at Sing's Restaurant in Bangor. More than sixty members attended. After cocktails and an exotic dinner, the meeting was opened by the President, Dr. David S. Beebe and the minutes of the December meeting were approved without addition or change. Dr. Beebe outlined the steps which will be taken to insure greater availability of medical services to the people of Penobscot County. Specifically, a telephone listing in the yellow pages by the Medical Society is planned. This service would make available the names of Society members who are accepting new patients. The February newsletter will include a brief form to be filled out by the interested physicians. It is hoped that the local media will cooperate in advertising this service.

A County Medical Directory was discussed and it was felt that both the format and the intended distribution of such a directory would require additional study before the committee could begin making specific recommendations.

Two new applications for membership were presented to the Society: Dr. Ali Khavari, a urologist practicing in Lincoln, and Dr. Brian Reilly, a Family Practice Specialist, were both unanimously elected to membership by written ballot.

The resolution concerning the $100.00 assessment for the new Maine Medical Association headquarters was approved by the membership after changing a few words which serve to further clarify the intent of the resolution. An additional resolution was discussed (as outlined in the January newsletter) which would provide equal representation for each County Medical Society on the Executive Committee of the M.M.A. It was voted to co-sponsor this resolution with the Executive Committee of the M.M.A. at the

House of Delegates meeting.

There was some discussion concerning the efficacy of continuing Scientific Sessions at our County Society meetings. It was felt that with the improved academic atmosphere in the County, the Scientific Sessions need not be included at County Medical Society meetings.

Members interested in serving on committees of the Maine Medical Association were urged to contact the County Secretary so that their names could be submitted to the Nominating Committee.

There being no further business, the meeting was adjourned.

The February meeting of the Penobscot County Medical Society was held at the Iron Kettle Restaurant in Brewer on February 20, 1979. Fifty members attended, including Mr. Frank O. Stred, the new Executive Director of the Maine Medical Association. After cocktails and dinner, the meeting was opened by the President, Dr. David S. Beebe and the minutes of the January meeting were approved without addition or change. The first topic to be discussed was the formation of a resolutions committee. It was felt that a standing committee of this type would be helpful. Drs. Frederick C. Emery, Robert J. Barrett, Jr. and Dexter T. Clough agreed to serve as members of the committee. It is felt that members could be added to the committee as necessary when resolutions are required.

Dr. Beebe reported on the questionnaires returned by the membership, and indicated that a yellow page listing is now available for public use. Efforts will be made to inform the public of this service.

One new application for membership was presented to the Society: Dr. Robert S. Leighton, an Anesthesiologist, practicing in Lincoln. He was unanimously elected to membership by written ballot.

Dr. Beebe presented information on the Cumberland County second opinion program and indicated to the membership that the Executive Committee felt that this would be a reasonable program for our Society to undertake. There was a very lively discussion with comments made by the membership and a report of the Cumberland County experience by Dr. Kittredge and Dr. Beebe. It was finally decided to discuss this further at the March meeting. By that time, a summary of the pertinent aspects of the program will be sent to the membership in the newsletter.

The new Executive Director of the Maine Medical Association, Mr. Frank O. Stred was then presented to the membership and he spoke briefly on his anticipated role in our State organization.

There being no further business, the meeting was adjourned at 9:00 p.m.

JAMES R. CURTIS, M.D., *Secretary*

Washington

A regular meeting of the Washington County Medical Society was held on January 23, 1979 at the Staff Room of the Down East Community Hospital, Machias, with fourteen members and guests present.

Dr. Henry F. Ryan, Chief Medical Examiner of the State of Maine, was introduced by the Washington County Medical Society President, Dr. James C. Bates of Eastport.

Dr. Ryan covered the duties of the Medical Examiner in the State of Maine. This was followed by slides, by Dr. Ryan, illustrating the various types of gunshot wounds and the method of identifying wounds of entrance and wounds of exit. Dr. Ryan stressed the importance of making use of the Sheriff and Police and County Attorney Dept. He also stressed the importance of proper identification of the deceased. Finger printing and dental examinations are most important in identification.

This was followed by questions from the audience. It was a most excellently presented coverage of the Medical Examiner System.

This was followed by the reading of the minutes of the last meeting, which were accepted, as read.

It was decided that all members of the Washington County Medical Society should be repolled on their feelings about Washington County Health Plan, and so designate. Once their wishes are known, a letter will be sent to Health, Education & Welfare in Boston, Massachusetts, as well as one to Washington County Health Plan, in East Machias.

Dr. Donald M. Robertson, Delegate to the Maine Medical Association, reported on the House of Delegates' meeting. This covered negotiating with Blue Shield, which has not been finalized, as yet. It also covered a new building for the Maine Medical Association and the steps that are being taken to set up a new headquarters. He also spoke about the negotiations of the M.M.A. and of the Osteopathic Association with the Department of Human Services. It is apparently possible, from court interpretations, to negotiate with the Department of Human Services, but this has to be done very carefully, without running into Anti-trust laws.

It was decided to have the next meeting March 13, 1979 at the Lincoln Inn, Dennysville.

KARL V. LARSON, M.D., *Secretary*

Kennebec

The Kennebec County Medical Association met at the Holiday Inn in Augusta on January 18, 1979 in the midst of a howling blizzard. There were 16 members and 5 guests, all members of the State legislature.

Following a very delicious rare roast beef dinner, there was a nice exchange of views between the legislators led by Senator Pierce and the members of the Association. The issues which were discussed included the patient's bill of rights, medical education, and the compact HMO's, the issues surrounding para professionals such as podiatrists and the issues surrounding chiropractic. The medical malpractice company, the Medicaid fee schedule issue and certificate of need issues were discussed. The members present felt that they had been able to contribute to a discussion with the legislators and the legislators seemed to feel that they had in fact gained from the discussion.

The meeting of the Kennebec County Medical Association was held at Guido's Wine Cellar in Augusta on March 15, 1979, with 48 members present.

A delicious roast beef dinner was enjoyed by all and no business was raised. Dr. H. Richard Hornberger gave to the Association the talk which he had presented to the graduating class at Tufts last year. His talk was well received by the members of the Association and a most pleasant evening was had by all.

O. THOMAS FEAGIN, M.D., *Secretary*

Lincoln-Sagadahoc

The regular monthly meeting of the Lincoln-Sagadahoc County Medical Society was held at The Ledges Inn, Wiscasset on February 20, 1979, with thirty-one members and guests present.

The meeting was called to order by the President, Dr. P. Richard Cote, and the minutes of the previous meeting were read by the secretary and accepted as read.

There being no old or new business proposed, the scientific portion of the meeting was held, with Drs. Haughwout and Darcy speaking on Treatment of Airway Emergencies.

GEORGE W. BOSTWICK, M.D., *Secretary*

Somerset

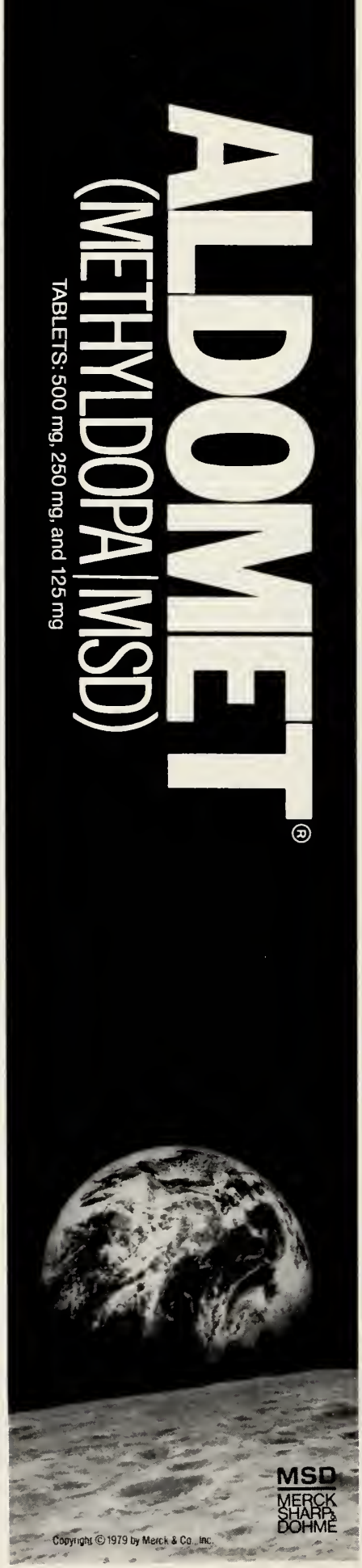
The regular meeting of the Somerset County Medical Society was held on February 13, 1979 at the Candle Light Restaurant in Skowhegan, with sixteen members present and four guest speakers from the Blues.

The meeting was called at about 6:00 p.m. by Dr. John H. Steeves, in the place of the President.

The secretary read the minutes of the last meeting. Dr. Iver Nielson made some correction of the last meeting previously attended by Dr. Phillips of Rumford.

The guest speakers from the Blues were presented by the Vice-President. Mr. Frank Faherty was the primary spokesman for the group with Messrs. Tim Joy, George Hansen, Sam Barouch and Powell. They presented structures and policies of the Blue Shield and discussed topics introduced by the Society members.

VINCENTE L. SY, M.D., *Secretary*



Androscoggin

The meeting of the Androscoggin County Medical Association was held at Chase Hall, Bates College on March 15, 1979. The meeting was called to order by the president, Dr. Lawrence A. Nadeau, with 52 members present.

The minutes of the previous meeting of February 1, 1979 were accepted.

The vice-president, Dr. Leo E. Cousineau, then introduced the guest speaker of the evening, Mr. William Sepe of Camden and his associate Mr. Steve Smith. These gentlemen are the architects of the proposed headquarters of the Maine Medical Association in Augusta. Mr. Sepe gave an illustrated talk regarding the plans and design of the structure. He then answered several questions. At the conclusion of the architect's presentation, Dr. Grimes introduced Mr. Frank Stred, the new Executive Director of the Maine Medical Association. Mr. Stred spoke for several minutes about the legislative problems facing the physicians in this State and then he discussed some of the financial implications of the new proposed headquarters in Augusta.

Dr. Charles W. Steele then read a resolution written in memory of Dr. John H. Busch.

The secretary read three pieces of correspondence. The first was a note from Mrs. J.J. Busch, expressing thanks for the County Society's memorial contribution. The second was a letter from Dr. Daniel A. Rock requesting a change in his status from active to affiliate member in the County Association. Then, there was a letter from Mr. Justin Cowger, Diabetes Project Director of Medical Care Development in Augusta. He requested that a member of the Androscoggin County Medical Association serve on the advisory committee of the diabetes project. The secretary suggested that physicians interested speak to him subsequently.

Committee reports were discussed. The report of the Advisory Committee was printed and distributed in full to the members present. Dr. Iain D. Sanderson made a few additional comments.

Dr. Nadeau then read the list of his appointees to the committees of the Maine Medical Association.

Dr. Frederick C. Holler spoke in behalf of the insurance committee. He noted that BC/BS group rates would increase for the members of the Association. He mentioned that negotiations with BC/BS were proceeding and that further news would be forthcoming at the June meeting of the House of Delegates. He also mentioned that the Medical Mutual Company, the doctors' malpractice insurance company, was "thriving."

Dr. Francis X. Fellers then spoke regarding PTO-PSR. He is involved in reviewing regional policy pertaining to certain hospitals in this area.

Under old business, a motion was removed from the table: motion to increase Androscoggin County Medical Association dues from $35.00 to $55.00 per year. This motion was approved virtually unanimously. (Note—this means an additional $20.00 assessment for this year 1979.)

Under new business, it was announced that the Public Relations Committee and Advisory Committee would merge, with Dr. Iain Sanderson serving as chairman. This group will be known as the Advisory Committee.

Dr. Thomas F. Shields then spoke regarding the relocation of the Association's office to a room being provided in the basement of the Bates College Infirmary. After some discussion of the benefits of a permanent location with mailing address and telephone, there was a unanimous vote in favor of this move.

The last item of new business was a renewed discussion of the proposed construction of the Maine Medical Association headquarters in Augusta. It was felt by some that the architectural and energy saving merits of the building were outweighed by deficiencies in the office layout. Other physicians objected to the image that the building would project and to its location. Most significantly, the finances and operating cost of the proposed headquarters were recognized as being more formidable than previously realized. A motion was then made to instruct the delegates to the April meeting to the Maine Medical Association to vote against the building as proposed. This motion was carried.

The meeting adjourned at 10:15 p.m.

EDWARD Z. WALWORTH, M.D., *Secretary*

ommittee on Continuing Medical Education Suggests Change in CME ystem -----

t its April 4 meeting the MMA's Committee on Continuing Medical ducation voted: "IN ORDER TO MEET HIS OR HER CONTINUING MEDICAL DUCATION OBLIGATIONS TO THE MAINE MEDICAL ASSOCIATION, A PHYSICIAN EMBER MUST DEMONSTRATE POSSESSION OF A PHYSICIAN'S RECOGNITION AWARD R ANOTHER NATIONALLY RECOGNIZED DISCIPLINARY CONTINUING MEDICAL EDUCA-ION REQUIREMENT."

ction on this Committee vote by the House of Delegates at the Annual eeting in June will be required before any change goes into effect.

n June 1, Governor Brennan signed into law LD 1502 which will make atisfactory evidence that "the applicant has completed a course of ontinuing medical education as prescribed in the rules and regulations f the board" a prerequisite to relicensure by the Board of Registration n Medicine, effective in July of 1982.

o Much for Self Regulation -----

ll physicians in the State as well as many other health professionals, usinessmen, association personnel and attorneys were invited by ttorney General Cohen to attend a one-day seminar on antitrust matters n Augusta on May 23. There was a sizable attendance.

ne Message of interest to associations was conveyed very strongly by a epresentative from the U.S.Justice Department at the beginning of the ession --- *The courts are not going to allow any professional self egulation. Any attempt to prevent interference in the patient/ ractitioner relationship by another practitioner through association aveats will not work and is dead by current court standards.*

ost Containment Begins At Home -----

fter discussion and negotiation between MMA and Blue Cross/Blue Shield f Maine, the company has agreed to receive direct payment from MMA's articipants in the Association's Blue Cross, Blue Shield and Blue lliance coverages.

his decision reflects a desire on the part of BC/BS to provide full ervice to MMA members and a business decision on the part of the Maine edical Association to try to use its personnel in those areas where it as the most expertise and can be of greatest assistance to the member-hip. It is, in short, an attempt at cost containment for the Associa-ion.

hile payments, beginning in November will be sent directly to BC/BS by ach MMA member, the Medical Association will continue to handle enroll-ent functions and out-of-cycle mailing of booklets, riders, etc.

ME Via Toll-Free Dialing -----

ontinuing medical education in obstetrics/gynecology and gastroenter-

keep physicians abreast of the latest developments in medicine--is now available to Maine physicians.

Developed by the Southern Medical Association under an educational grant from Ortho Pharmaceutical Corporation, the Dial Access system uses tape recorded messages from noted medical authorities accessable through a toll-free telephone number.

Dial Access has been approved for continuing medical education credit by the American Medical Association and the American College of Obstetricians and Gynecologists. The programs are available nationwide through 1-800-633-4560. One hundred tapes of 8-10 minute problem-oriented messages representing the latest diagnostic and therapeutic practices have been prepared in ob/gyn and gastroenterology. Ob/gyn programs were developed by the Department of Obstetrics/Gynecology, University of Southern California School of Medicine; and Women's Hospital, Low Angeles County, California. Gastroenterology programs were developed at Emory University School of Medicine, Atlanta, GA.

Brochures listing the programs can be obtained from Thomas H. Andrykovitz, Product Director, Educational Programs, Ortho Pharmaceutical Corporation, Raritan, New Jersey 08869.

Medical Control of Blue Shield May Be Subject of Rule Making -----

The Federal Trade Commission staff has recommended that the Commissio open a rule making proceeding to look at whether the "medical physicians" control of Blue Shield and other similar medical plans violates Federal antitrust laws.

The proceedings proposed by the FTC Bureau of Competition would focus on a rule that would prohibit physician organizations from participating in the control of such plans. The staff recommendation came as part of a 409-page report that is the product of a 3-year investigation by the Bureau of Competition into the extent, impact, and legality of medical control of Blue Shield and similar plans. The report marks the first time the Commission staff has recommended rule making as a means of antitrust enforcement.

The report notes that in documents received during the investigation, medical societies referred to Blue Shield as the "economic arm of the medical profession." The report concludes that some forms of medical participation in control of Blue Shield and other plans may be illega as violations of the antitrust laws and as unfair conflicts of intere

Woodchuck May Be New Model For Hepatitis Research -----

According to the National Society for Medical Research, a new and less expensive animal model for hepatitis research has been discovered in the woods of Pennsylvania--the woodchuck. Because of a peculiar ruling on woodchuck trapping, however, it may be a while before they become readily available to research facilities.

Three Pennsylvanians started a woodchuck farm last year to supply healthy animals to hepatitis researchers, but have to buy their supply from out of state because the Pennsylvania Game Commission allows hunters to trap woodchucks for killing, not for selling for profit.

Regulations, Regulations, Regulations

When the indications surface...



NEOSPORIN® Ointment
(Polymyxin B-Bacitracin-Neomycin)

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
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Each gram contains: Aerosporin® (Polymyxin B Sulfate) 5,000 units, bacitracin zinc 400 units, neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base), special white petrolatum qs; in tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

INDICATIONS: *Therapeutically,* (as an adjunct to systemic therapy when indicated), for topical infections, primary or secondary, due to susceptible organisms, as in: infected burns, skin grafts, surgical incisions, otitis externa; primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia); secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis); traumatic lesions, inflamed or suppurating as a result of bacterial infection. *Prophylactically,* the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components. Do not use in the eyes or in the external ear canal if the eardrum is perforated.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

The Maker

Examining a Few Myths About Prescribing.



Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand-name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to a reference product. As you know, there is substantial literature on this subject affecting many drugs, including such antibiotics as tetracycline and erythromycin. The record on drug recalls and court actions affirms strongly that there are differences among pharmaceutical companies and their products. Research-intensive companies have far better records than those that do no research and may practice minimum quality assurance.

MYTH: Industry favors only "expensive" brand names and denigrates all generics.

FACT: PMA companies make 90 to 95 percent of the drug supply, including, therefore, most of the generics. Drug nomenclature is not the important point; it's the competence of the manufacturer and the integrity of the product that count.

Matters.

MYTH: Generic options almost always exist.

FACT: About 55 percent of prescription drug expenditure is for single-source drugs. This means, of course, that for only 45 percent of such expenditure, is a generic prescribing option available.

MYTH: Generic prescriptions are filled with inexpensive generics, thus saving consumers large sums of money.

FACT: Market data show that you invariably prescribe—and pharmacists dispense—both brand and generically labeled products from known and trusted sources, in the best interest of patients. In most cases the patient receives a proven brand product. Savings from voluntary or mandated generic prescribing are grossly exaggerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

PMA

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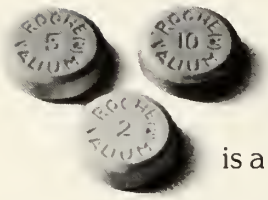
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But the individual character of Valium is even more apparent clinically than pharmacokinetically. And far more significant. That's because of the patient response obtained with Valium. A response which brings a calmer frame of mind. A response which has a pronounced effect on the somatic symptoms of anxiety, particularly muscular tension. A response which helps the patient feel more like himself again because of the way Valium reduces the overwhelming symptoms of anxiety and psychic tension.

Another important aspect of the clinical character of Valium is safety. Though drowsiness, ataxia and fatigue are possible, these and more serious side effects are rarely a problem. Of course, as with all CNS-acting drugs, patients taking Valium should be cautioned against driving, operating dangerous machinery or the simultaneous ingestion of alcohol.

Unquestionably, many psychotherapeutic agents, including other benzodiazepines, have antianxiety effects. But one fact remains: you get a certain kind of patient response with Valium. It's a response you want. A response you know. A response you trust as part of your overall management of anxiety and psychic tension.

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Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).
The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.

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A reminder

ZYLOPRIM®
(allopurinol)

100 and 300 mg scored Tablets

- inhibits uric acid formation
- helps prevent urate crystal depositions in synovia
- reduces risk of uric acid lithiasis

INDICATIONS AND USE: This is not an innocuous drug and strict attention should be given to the indications for its use. Pending further investigation, its use in other hyperuricemic states is not indicated at this time.

Zyloprim® (allopurinol) is intended for:

1. treatment of gout, either primary, or secondary to the hyperuricemia associated with blood dyscrasias and their therapy;
2. treatment of primary or secondary uric acid nephropathy, with or without accompanying symptoms of gout;
3. treatment of patients with recurrent uric acid stone formation;
4. prophylactic treatment to prevent tissue urate deposition, renal calculi, or uric acid nephropathy in patients with leukemias, lymphomas and malignancies who are receiving cancer chemotherapy with its resultant elevating effect on serum uric acid levels.

CONTRAINDICATIONS: Use in children with the exception of those with hyperuricemia secondary to malignancy. The drug should not be employed in nursing mothers.

Patients who have developed a severe reaction to Zyloprim should not be restarted on the drug.

WARNINGS: ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme) and very rarely a generalized vasculitis which may lead to irreversible hepatotoxicity and death.

A few cases of reversible clinical hepatotoxicity have been noted and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. Accordingly, periodic liver function tests should be performed during the early stages of therapy particularly in patients with pre-existing liver disease

Patients should be alerted to the need for due precautions when engaging in activities where alertness is mandatory.

Nevertheless, iron salts should not be given simultaneously with Zyloprim. This drug should not be administered to immediate relatives of patients with idiopathic hemochromatosis.

In patients receiving Purinethol® (mercaptopurine) or Imuran® (azathioprine), the concomitant administration of 300-600 mg of Zyloprim per day will require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of Purinethol or Imuran should be made on the basis of therapeutic response and any toxic effects.

Usage in Pregnancy and Women of Childbearing Age. Zyloprim® (allopurinol) should be used in pregnant women or women of childbearing age only if the potential benefits to the patient are weighed against the possible risk to the fetus.

PRECAUTIONS: Some investigators have reported an increase in acute attacks of gout during the early stages of allopurinol administration, even when normal or subnormal serum uric acid levels have been attained.

It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. This interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

A fluid intake sufficient to yield a daily urinary output of at least 2 liters and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable to (1) avoid the theoretic possibility of formation of xanthine calculi under the influence of Zyloprim therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Patients with impaired renal function require less drug and should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in renal function appear.

In patients with severely impaired renal function, or decreased urate clearance, the half-life of oxipurinol in the plasma is greatly prolonged. Therefore, a dose of 100 mg per day or 300 mg twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels. Such patients should be treated with the lowest effective dose, in order to minimize side effects.

Mild reticulocytosis has appeared in some patients.

As with all new agents, periodic determination of liver and kidney function and complete blood counts should be performed especially during the first few months of therapy.

ADVERSE REACTIONS:

Dermatologic: Because in some instances skin rash has been followed by severe hypersensitivity reactions, it is recommended that therapy be discontinued at the first sign of rash or other adverse reaction (see WARNINGS). Skin rash, usually maculopapular, is the adverse reaction most commonly reported.
Exfoliative, urticarial and purpuric lesions, Stevens-Johnson syndrome (erythema multiforme) and toxic epidermal necrolysis have also been reported.
A few cases of alopecia with and without accompanying dermatitis have been reported.
In some patients with a rash, restarting Zyloprim (allopurinol) therapy at lower doses has been accomplished without untoward incident.

Gastrointestinal: Nausea, vomiting, diarrhea, and intermittent abdominal pain have been reported.

Vascular. There have been rare instances of a generalized hypersensitivity vasculitis or necrotizing angiitis which have led to irreversible hepatotoxicity and death.

Hematopoietic: Agranulocytosis, anemia, aplastic anemia, bone marrow depression, leukopenia, pancytopenia and thrombocytopenia have been reported in patients, most of whom received concomitant drugs with potential for causing these reactions. Zyloprim® (allopurinol) has been neither implicated nor excluded as a cause of these reactions.

Neurologic. There have been a few reports of peripheral neuritis occurring while patients were taking Zyloprim. Drowsiness has also been reported in a few patients.

Ophthalmic: There have been a few reports of cataracts found in patients receiving Zyloprim. It is not known if the cataracts predated the Zyloprim therapy. "Toxic" cataracts were reported in one patient who also received an anti-inflammatory agent; again, the time of onset is unknown. In a group of patients followed by Gutman and Yü for up to five years on Zyloprim therapy, no evidence of ophthalmologic effect attributable to Zyloprim was reported.

Drug Idiosyncrasy. Symptoms suggestive of drug idiosyncrasy have been reported in a few patients. This was characterized by fever, chills, leukopenia or leukocytosis, eosinophilia, arthralgias, skin rash, pruritus, nausea and vomiting.

OVERDOSAGE: Massive overdosing, or acute poisoning, by Zyloprim has not been reported.

HOW SUPPLIED: 100 mg (white) scored tablets, bottles of 100 and 1000; 300 mg (peach) scored tablets, bottles of 30, 100 and 500. Unit dose packs for each strength also available.

Complete information available from your local B. W. Co. Representative or from Professional Services Department PML.

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of the
Maine Medical Association

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Total Knee Arthroplasty: A Five-Year Retrospective Study

Rowland W. Pritchard, M.D.

Introduction

Long term success with the total hip joint prosthesis has led to the development of prosthetic knee implants for the treatment of deformity and pain secondary to the degenerative changes of arthritis. Initial designs of knee implants featured replacement of the weight bearing surfaces of the distal femur and the proximal tibia, using high molecular weight polyethylene articulated against a cobolt chrome alloy. These early designs for the most part ignored the patellofemoral articulation which also is usually involved by the arthritic process. As a result of the failure to replace the patella, a certain percentage of patients undergoing this type of arthroplasty procedure noted post-operative pain and disability relating to the patellofemoral articulation. Over the past seven years, these prostheses have been refined to the point that current designs allow for the replacement of all three compartments of the knee joint (Fig. 1), that is the medial, the lateral and the patellofemoral compartments. The non-constrained version of the three compartmental type total knee replacement is now exceedingly popular with orthopaedic surgeons across the country. This anatomic knee design replaces the distal femoral condyles, the tibial plateau with or without cruciate ligament retention, and the patellofemoral articulation. A number of these anatomic knee prostheses are currently available on the market. In the author's experience, use of the non-constrained anatomic knee prothesis when adhering to strict surgical principles, provided relief of pain and restoration of function.

Material

One hundred and twenty anatomic total knee replacements have been carried out by the author over the past five years at the St. Joseph's Hospital in Bangor, Maine. The presenting complaint in all but two cases was that of pain, uncontrolled by analgesics. Deformity, instability and loss of function were the overwhelming secondary complaints voiced at the time of surgery. The primary diagnosis in one hundred cases was that of degenerative osteoarthritis. This group was composed of sixty-nine females with an average age of 67.7 years and thirty-one males with an average age of 66.6 years. The oldest patient in this category was a 91-year-old female in excellent medical condition with the solitary complaint of a severely deformed right knee. The youngest patient in this series was a 42-year-old female suffering from post-traumatic degenerative arthritis of the knee. The remaining patients include fifteen females and five males with the diagnosis of disabling rheumatoid arthritis.

Indications for Surgery

Although severe destructive bony changes were noted in all cases by x-ray examination, the primary indication for total knee arthroplasty as viewed by the author was that of pain unrelieved by analgesics or anti-inflammatory medications. Joint instability and loss of function were considered secondarily. Old age, per se, was not considered to be a contraindication to this type of surgery. The physiologic and mental condition of the patient was felt to be far more impotant than the chronologic age. In the osteoarthritis group, fifteen patients were 80 years of age or older at the time of their surgery. Presently, all of those patients with one exception are alive and ambulating without external supports.

Contraindications for Surgery

Prosthetic replacement of the knee joint was felt to be contraindicated in patients with a previous or current history of joint sepsis. Youthful patients with severe arthritis were treated with tibial osteotomies rather than total joint arthroplasty due to the concern of increased loosening of the implant secondary



Fig. 1



Fig. 2



Fig. 3

Fig. 1. Shaded areas representing a three compartmental total knee replacement in a lateral view.

Fig. 2. Preoperative AP x-ray showing lines of bone resection in a varus deformity.

Fig. 3. Enviracon Air Filter unit in background of operating room.



Fig. 4



Fig. 5

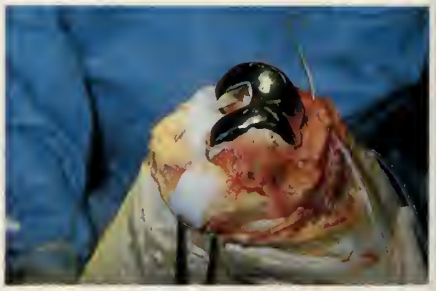


Fig. 6

Fig. 4. Dorsal view of knee in extension. Solid line (A) marks mid-line skin incision. Dotted line (B) represents deep tissue incision into the knee joint.

Fig. 5. Knee joint flexed and opened with patella everted and reflected laterally. Hemostat points to areas of total cartilage loss on medial femoral condyle.

Fig. 6. Three component parts of the Townley anatomic knee prosthesis after cement fixation.

to over-use of the joint by the patient. No patients with neurotrophic joints were accepted for total knee replacement. The patients with severe arthritic knees who fell into the category of poor surgical risks due to serious medical problems were not considered for this surgery.

Surgical Technique

All patients were admitted to the hospital at least two days prior to the surgery and underwent an extensive medical evaluation preoperatively by an internist in order to treat associated medical problems. Preoperative weight bearing x-ray films of the knees were used at the time of surgery to determine the amount of bone to be resected from the distal femur and proximal tibia (Fig. 2). Preoperative antibiotics in the form of two grams of intravenous Oxacillin or Keflin® were given to all patients two hours prior to surgery. Short duration spinal anesthesia was preferred and used routinely (one hundred and five cases) unless contraindicated by pre-existing neurologic problems or the patient's refusal to accept a spinal. All cases were performed in an Enviracon® filtered air flow chamber (Fig. 3) in order to reduce particulate contamination during surgery. A pneumatic tourniquet was inflated to five hundred mms. of mercury and used for hemostasis during the surgery in all cases. The average tourniquet time was one hour and thirty minutes with an average surgical time of approximately one hour and fifteen minutes. The surgical exposure was obtained through a mid-line incision made from the tibial tubercle to the suprapatellar pouch region (Fig. 4). The underlying medial retinacular structures were then incised so as to place the skin incision and the underlying deep tissue incision approximately one and a half to two cms. apart. (It is the author's feeling that this type of surgical approach lessens the chance of a deep infection developing within the knee joint should there be superficial infection of the skin incision postoper-

atively due to skin contaminants.) After incising the medial retinacular structures, the patella was everted and reflected laterally so that the knee joint could be placed in hyperflexion for the necessary bone resection of the distal end of the femur and the proximal tibia (Fig. 5). After a trial reduction with the prosthetic components in place, all three components, the distal femoral component, the tibial plateau component and the polyethylene undersurface of the patella, were simultaneously cemented in place (Fig. 6). Release of the lateral patellar retinacular ligaments and reefing of the medial patellar retinacular ligaments was usually carried out in order to prevent lateral subluxation of the patella postoperatively. A medium sized hemovac drain was inserted into the joint space in all cases and maintained on high wall suction for a period of forty-eight to seventy-two hours. Postoperative intravenous antibiotic therapy was continued for seventy-two hours, administering an average of one gram of Oxacillin or Keflin every six hours. After discontinuation of the intravenous therapy at seventy-two hours, the patient was maintained on oral antibiotics until wound healing was complete. Usually after three days, the patient was begun ambulating with a walker and gradually progressed to Loftstrand® short arm crutches. Immobilization of the knee following surgery was accomplished with an adjustable soft extension splint. Gentle flexion exercises were initiated by the physical therapy team usually on the fifth postoperative day. Independent walking and stair climbing was accomplished as a rule by the twelfth to fourteenth postoperative day. Hospital discharge was usually possible two weeks after surgery. Older persons often required an additional two to three weeks in an extended care facility after discharge before returning home.

Results

Freedom from pain was the primary end result sought after in all one hundred and twenty cases. In follow-up ranging from three to fifty-eight months, it was noted that all patients claimed a dramatic relief of their preoperative pain. The patients were routinely seen at three week intervals for the first three postoperative months. After that point, they were reviewed on a once a year basis. At the time of this review, the patients were questioned in regard to the presence or absence of pain; the presence or absence of instability of the knee joint and patella; and the patient's general overall impression regarding their surgery and knee function. At the same time, x-rays were taken to ascertain whether or not loosening of the component parts was radiographically visible.

Although full extension as well as flexion of at least 90 degrees or greater was sought, as an end result, a small percentage of patients did not obtain these goals. Lack of full extension in the range of -10 to -20 degrees was noted in six cases associated with severe preoperative flexure contractures and varus deformities. It is interesting to note that the most frequent deformity encountered in both the osteoarthritic and the rheumatoid groups was a varus angulation (bow leg) often associated with a flexure contracture. These deformities were highest in the female osteoarthritic group and usually associated with exogenous obesity. Adequate flexion so as to allow stair climbing was achieved in all but two cases of this series. The vast majority of patients obtained flexion in the range from 90 to 110 degrees postoperatively. When 90 degrees of flexion was not achieved by the fourteenth postoperative day, manipulation of the knee joint was undertaken in the hospital under intravenous pentathol anesthesia. Such manipulation was required for fifteen percent of the reported cases.

Complications

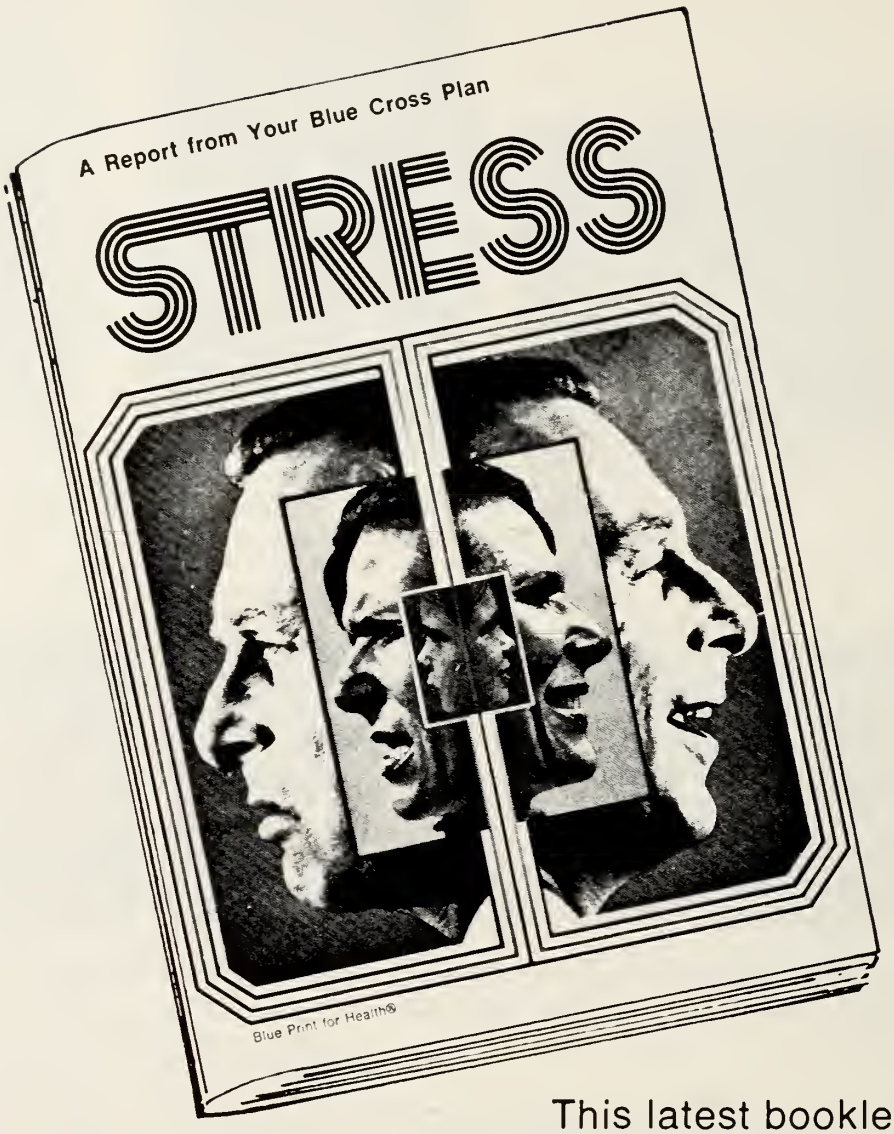
The two major complications associated with total joint replacement are postoperative infection of the prosthesis and long-term loosening of the bone-cement fixation. In this series of one hundred and twenty cases with the maximum five year follow-up, no clinical or radiographic evidence of loosening of the prosthetic implant has been encountered. Four postoperative deep wound infections have been noted in this series. All of these cases occurred in severe rheumatoid patients having been maintained on greater than physiologic doses of steroids, both pre- and postoperatively. Two of these cases could not be controlled with oral antibiotics and required eventual removal of the prosthesis and fusion of the knee joint. Of the two remaining cases, one has been re-operated upon, debrided and currently has been free of infection for the past year and a half. The fourth case of infection developed in an elderly gentleman who retained his implant but required daily oral antibiotics in order to prevent active drainage from a sinus tract in the surgical incision. Three years after surgery while still on oral antibiotics the patient died of an apparent non-related myocardial infarction. During his regular visits over that three year period, however, in spite of the chronic infection, the patient maintained that his knee joint was free of pain.

Lesser complications were associated with lateral subluxation of the patella in three cases; avulsion of the infrapatellar tendon from the tibial tubercle in two cases; and fracture of the patella with loss of fixation of the patellar prosthesis in two cases following direct trauma. Both of these latter two cases required re-operation with removal of the patellar prosthesis and debridement of the patellar fragments.

Summary

The results of one hundred and twenty anatomic total knee replacements carried out by the author over the past five years suggest that a dramatic relief of pain was obtained using this surgical treatment for cases of severe rheumatoid or degenerative osteoarthritis involving the knee joint. Improved knee function was noted as well in the vast majority of these

Continued on Page 264



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Myocardial Infarction in a Rural Maine Hospital

Robert W. Sucsy, M.D.

Abstract

Effective care for acute myocardial infarction is given at a twenty-four (24) bed "Down East Maine" hospital. Routine Coronary Care Unit monitoring tempered by time honored nursing care and non-invasive medical care resulted in a mortality rate as low as the lowest national average.

"Thinking big" in medicine may result in astronomical cost increases without appreciable benefits to the patient.

Introduction

The mortality rate for acute myocardial infarction, in-hospital, is variously reported as from 15-52% with an average of 33% before Coronary Care Unit (CCU). Post CCU the figures have fallen to from 15-26%.

There continues to be controversy regarding therapy as techniques requiring higher degrees of technical skill are used. These techniques usually representing the invasive modalities such as Swan-Ganz catheter, cardiac pacemakers, aortic balloon pump, etc.

There remains in medicine, as in everything else, the "Law of Diminishing Return." With rapidly escalating costs, medicine, as well as society, must concern itself with results measured against effort.

In reply to this challenge, the mortality rate as a measure of the level of cardiac care is reported from a twenty-four (24) bed rural Maine seacoast hospital.

The staff consists of three (3) family practitioners, a general surgeon and general internist. General duty nursing personnel with electrocardiographic (EKG) and cardiopulmonary resuscitation (CPR) training, staff the CCU. EKG monitoring, electroshock defibrillator, CPR equipment, and standard cardiac drugs are available. Laboratory, X-Ray and EKG studies are available on a 24-hour basis with emergency EKG dataphone consultation. Patients are admitted to the CCU and are cared for by the family physician.

For comparison, statistics from the same institution are presented for the years 1969 and 1977.

Hospitalized Acute Myocardial Infarction 1977

Total Patients	29
Deaths	5
% Mortality	17.3
CCU-Length of Stay	3.6
Average Hospital Stay	14.6
Average Patient Age (Range 48-89)	72

Diagnosis

Two patients deceased on admission, but included in the study, had no EKG or cardiac enzyme record other than a "rhythm strip".

Six patients had typical symptoms and positive diagnosis either by EKG or cardiac enzymes. All others had positive history, physical, EKG and cardiac enzyme findings.

CPR With Electroshock

One—Acute ventricular fibrillation. Recovered. Age 48.

One—Cardiovascular collapse prior to admission. One hour of CPR. Deceased. Age 72.

One—Ventricular tachycardia third day post myocardial infarction. Deceased. Age 63.

One—Ventricular fibrillation twenty (20) minutes post admission. Deceased. Age 70.

Arrhythmias

Premature ventricular contractions most common. Otherwise the entire gamut of atrial and ventricular arrhythmias were represented.

Drugs

Commonly Used	*Rarely Used*
lidocaine	atropine
nitroglycerin	dopamine Hcl
diazepam	sodium bicarbonate
morphine	pronestyl
furosemide	heparin
quinidine	aminophylline
isosorbide dinitrate	adrenalin Hcl
propanolol	hydralazine Hcl
digoxin	
potassium chloride	
2% nitroglycerin ointment	

Transfers

One transfer to a Veterans Administration hospital for follow-up care of acute manic depressive psychosis, twenty (20) days post myocardial infarction.

Other Therapeutic or Diagnostic Modalities

There were no cardiovascular invasive techniques.

Ultrasound is not available as a diagnostic modality.

Secondary Complications

Every patient had one or more complicating medical problems including:

(1) Pulmonary embolism
(2) Congestive heart failure
(3) Hypertension

(4) Cardiac arrhythmias
(5) Diabetes mellitus
(6) urinary tract infection
(7) Acute cerebrovascular accident
(8) Previous myocardial infarction

Hospitalized Acute Myocardial Infarction 1969

Total Patients	21
Deaths	7
% Mortality	33%
Average Hospital Stay	16 days
Average Patient Age	64.5 years

A review of 1969 acute myocardial infarctions indicated that there existed approximately the same conditions of medical care but the use of intensive care facilities with monitoring were not absolutely routine.

In particular, lidocaine was not used nor was nitroglycerin ointment. Other minor differences in drug therapy were probably not significant except for the almost routine use of heparin and warfarin.

Lidocaine by both IV bolus and IV infusion for the very frequent complication of premature ventricular contractions stands out as the only common drug innovation.

Summary

The mortality rate of 17.3% for acute myocardial infarction at a twenty-four (24) bed rural primary care hospital is presented as evidence that excellent medical care can be provided with a modicum of medical expertise and hardware.

The factors of prompt medical attention in a friendly home town hospital environment may weigh heavily in the patients' favor.

The mortality rate improvement from 33% in 1969 to 17% in 1977 speaks for itself as representing the influence of *routine* CCU treatment for acute myocardial infarction.

Blue Hill Memorial Hospital, Blue Hill, Maine 04614.

Total Knee Arthroplasty: A Five-Year Retrospective Study

Continued from Page 261

patients postoperatively. Postoperative complications have been few but nevertheless did include a three percent infection rate. No loosening of implants has been noted to date.

80 Broadway, Bangor, Maine 04401

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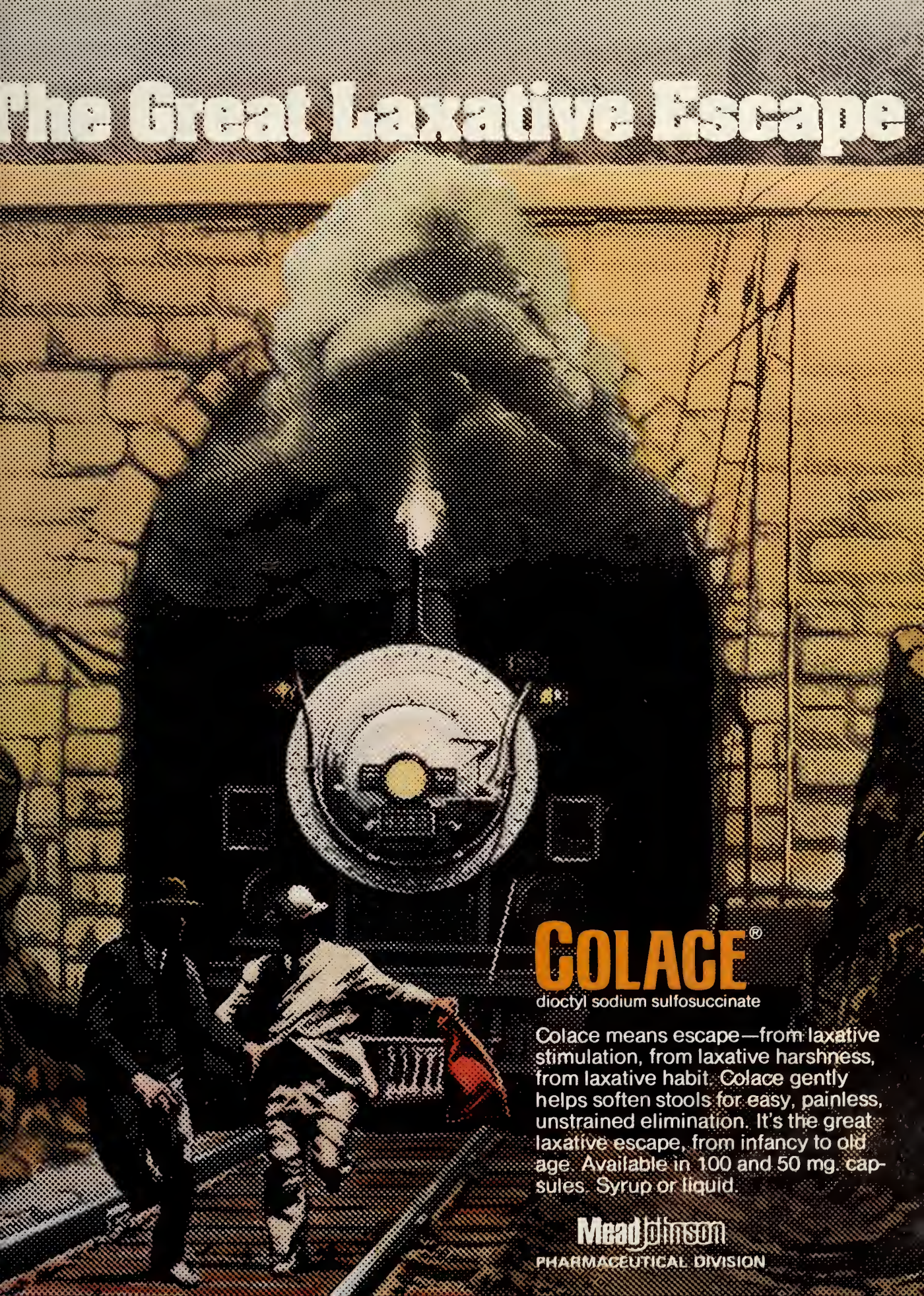
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The Maine Medical Association's House of Delegates, at its June 1976 meeting, adopted a regulation stating that a *minimum of 150* hours of continuing medical education is required in order to maintain membership. The policy took effect on January 1, 1977 and all members must be certified by January 1, 1980. Eligibility for certification begins January 1, 1977.

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Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

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Intravenous administration should not be given because of increased likelihood of side effects.

Adverse Reactions: On rare occasions oral administration of the drug has been associated in time with the occurrence of hypotension, tachycardia, nausea, vomiting, dizziness, abdominal distress, and severe rash. If rash appears the drug should be discontinued.

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The Pragmatic Approach to Carcinoma of the Lung

Saul Katz, M.D.*

Cancer of the lung is now the most frequent cause of death from cancer in men. The mortality rate has increased twenty-five-fold in the last 45 years and there has been a dramatic rise in the incidence in women as well.[1] In Maine there will be more than 500 cases this next year and the number can be expected to increase in a population addicted to cigarettes.

Many patients present to their physicians late in the course of the disease. There may be further delay because of difficulties in recognition, diagnosis, and selection of therapy.

Evaluation and care of these patients should be guided by principles based on the natural history and biologic patterns of lung cancer. These are conveniently expressed as five aphorisms:

1. The symptoms of lung cancer are not specific but most patients are symptomatic.

The initial symptoms of lung cancer in order of occurrence are cough 41%, chest pain or discomfort 22%, hemoptysis 6%, respiratory infection 6%, malaise 4%, weight loss 4%, dyspnea 2%, and hoarseness 2%.[2] With the exception of hemoptysis, these symptoms are protean and easily attributed to other causes or even ignored.

Cough is the most important lung cancer warning sign. It may be new, or more commonly, there is a change in the character of a chronic cough. The morning "cigarette" cough may be replaced by a dry irritating hack that persists throughout the day. Conversely, in some patients, sputum production may be increased or there may be a change in the color or thickness of the sputum. These changes may not be obvious to the patient but can be elicited by a careful history.

Hemoptysis, although an infrequent initial symptom, is a common presenting complaint because it is frightening to the patient and his family. It usually consists of small flecks or streaks of blood in the first raised sputum of the day and may disappear for days or weeks at a time.

Upper or lower respiratory infections that do not resolve completely in a matter of weeks may be a manifestation of an underlying lung cancer.

Although 2 to 3% of lung cancer patients are truly asymptomatic and another 4 to 5% will present with central nervous system, endocrinologic or other distant manifestations of their disease, the vast majority will have one or more chest symptoms due to local effects of the tumor.

2. Surgical removal of the tumor and the involved nodes is the best chance for cure.

Surgery has remained the mainstay of lung cancer therapy since the first successful pneumonectomy in 1933.[3] The operative mortality is low and the overall five-year survival of resected patients is 25-30% and approaches 60% in the most ideal subgroups.[4]

3. Tissue type and extent of tumor determine the chance of cure and susceptibility to palliation.

Squamous carcinoma affords a better opportunity for surgical cure than adenocarcinoma and undifferentiated large cell carcinomas. Within each cell type the prognosis is better for the well differentiated tumors than the less differentiated ones.[5] Small cell undifferentiated or "oat" cell tumors are the most ominous variety of lung cancer and here chemotherapy and radiotherapy have replaced surgery as treatment.

The clinical stage of a lung cancer is determined by the size and extent of the tumor, nodal involvement, and the presence or absence of metastatic disease. The patient's clinical stage is predictive of the chance for cure. If he is inoperable for medical reasons, the clinical stage is predictive of the response to radiation therapy. Some patients, who are unresectable, may be candidates for attempted cure by radiotherapy. The knowledge of both clinical stage and tissue type permits a very accurate estimate of the patient's prognosis.[6]

4. Most patients are incurable at the time of diagnosis.

Lung cancer grows insidiously and causes symptoms late in its course. At presentation, 30% of patients have spread of tumor to regional organs and lymph nodes beyond the scope of resection.[7] Another 50% have distant metastases. Therefore, only 20% are potentially curable at the time of discovery.

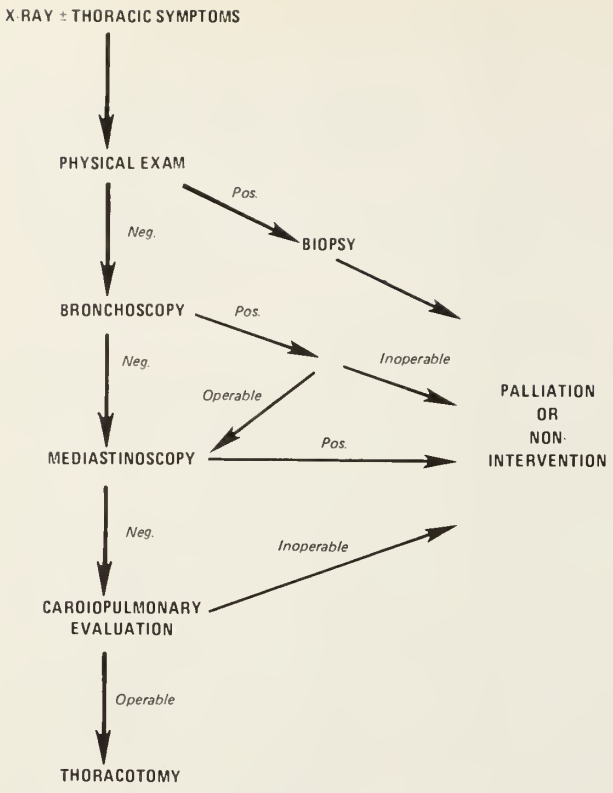
5. Patients with incurable lung cancer have a limited life expectancy.

Of those patients who are either inoperable or are operated upon but are unresectable, 90% are dead within one year.[8] Only 1% survive for two years. Many, however, can be made comfortable and their symptoms ameliorated by palliative therapy.

It is apparent from the preceding discussion that smokers should be questioned about cough, chest pain, hemoptysis, upper respiratory infection, dyspnea, malaise, weight loss, etc., at each physician contact and a chest x-ray obtained when a suspicion of possible lung cancer arises. Once the diagnosis becomes likely, the primary goal is the early iden-

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Decision making in suspected lung cancer

tification and therapy of the 20% of patients who are potentially curable. The remaining 80% of patients are also best served by prompt diagnosis and staging so that their remaining days are not squandered in the hospital and appropriate treatment can be initiated.

A pragmatic approach to the patient with suspected lung cancer may be achieved by organizing the essential diagnostic and therapeutic choices into a sequence of five steps. At each step an attempt is made to answer three basic questions:

1. IS THE DIAGNOSIS CONFIRMED BY HISTOLOGY?
2. WHAT IS THE DOCUMENTED EXTENT OF DISEASE?
3. IS THE PATIENT A CANDIDATE FOR CURE, PALLIATION, OR NONINTERVENTION?

Step 1—Physical and Laboratory Examination

Evidence of obvious metastatic disease is sought. Palpable cervical or scalene nodes or subcutaneous nodules can be biopsied under local anesthesia in the out-patient department. Palpable hepatic lesions can be approached transcutaneously under local anesthesia in the hospital. If any of the above are positive, the patient has an advanced stage of cancer and is inoperable. He may then be considered for palliative therapy or, if appropriate, nonintervention for the time being. Abnormal liver chemistries and serum calciums may be indicative of metastatic disease.

Step 2—Bronchoscopy

This may be performed under topical anesthesia, and if convenient, in the out-patient department. Facility with both the rigid bronchoscope and the flexible fiberoptic instrument provides the maximum opportunity to visualize the malignant lesion and obtain tissue or cells for diagnosis. The surgeon is also interested in the location and proximal extent of the tumor in order to determine if it is operable and whether a lobectomy or pneumonectomy will be likely. The appearance of the carina is important as it may be broadened by subjacent malignant lymph nodes. The condition of the bronchial mucosa can give some clue to the likelihood of postoperative respiratory complications. If "oat" cell carcinoma is found, or the tumor is inoperable by virtue of its location, or if a tissue diagnosis is made but the patient is found to be inoperable for medical reasons, no further surgical intervention is needed.

Step 3—Mediastinoscopy

This procedure is performed in the operating room under general or local anesthesia through a 5 to 6 cm low transverse cervical incision. The patient may be discharged the following day. The lymph nodes adjacent to the trachea, carina, and proximal right main stem bronchus can be visualized and biopsied. If they are free of metastases, the patient remains a candidate for cure. In some circumstances, patients with limited metastases to low ipsilateral mediastinal nodes may be considered candidates for attempt at cure as well.

Step 4—Cardiopulmonary Evaluation

The surgeon must assess the patient's cardiac and pulmonary reserves to determine whether his condition will permit the proposed resection. This determination is not reducible to simple formulae nor is it facilitated by elaborate testing. It is based on an overall evaluation of the patient's medical condition, physical examination, functional status, exercise tolerance, mental attitude, and the surgeon's past experience. The lesion may be determined inoperable because of severe heart disease or disabling pulmonary disease and either nonintervention or palliative therapy offered instead of surgery.

Step 5—Thoracotomy

If the patient has met the criteria of steps 1-4 for operability, he should undergo thoracotomy without delay. Ninety percent of patients thus screened will be able to undergo resection for cure. About ⅓ will require pneumonectomy and the remainder will be well treated by lobectomy.

Other Tests

There are a number of additional frequently performed and sometimes superfluous diagnostic procedures several of which are worth discussion.

Sputum Analysis

The chance of diagnosis by examination of an ideally collected sputum sample is 20-40% and improves with the number of samples examined.[9] The

collection process is time consuming and expensive if it prolongs the stay of a hospitalized patient. Frequently the specimen is less than ideal. Most patients will require bronchoscopy anyway and the latter is more likely to yield a diagnosis. Furthermore, sputum collected during the first two hours after bronchoscopy has a particularly high diagnostic yield.[10]

Radioisotope Imaging

Liver, brain, and bone scans are not helpful in the patient with potentially curable disease. In the absence of clinical or laboratory evidence of involvement of these organs, routine scans are unlikely to detect metastatic disease and there is a considerable incidence of false-positives.[11] Scanning is of value in patients with probable metastatic disease and in planning palliative therapy for patients with unresectable tumors.

Scalene Fat Pad Biopsy

In the absence of palpable nodes extirpation of the scalene fat pad is not of value. Only 12% of patients with lung cancer have scalene metastases and almost one-half of patients with negative biopsies prove to have unresectable tumors.[12] Mediastinoscopy is preferable because it reaches nodes more proximal in the lymphatic chain and has been found positive in 28% of patients with negative scalene nodes.[13]

Needle Aspiration

Percutaneous aspiration under fluoroscopic control of peripheral lung lesions is of great value in patients with inaccessible metastatic disease or those who are otherwise judged inoperable. It can provide these individuals with expeditious one step outpatient diagnosis. The procedure, however, is infrequently of value in potentially curable disease. If the aspirate is not diagnostic of malignancy then thoracotomy will be advised and, if it is positive, thoracotomy will also probably be advised. The chance of discovering a peripheral "oat" cell carcinoma is less than 5% and in this location it is probably no less curable than any other histologic type.[14]

Summary

In the absence of good methods of detection of lung cancer in the asymptomatic stage, earlier recognition is dependent on the interest and ability of the physician to consider and pursue the diagnosis. In suspected cases an expeditious workup should proceed guided by knowledge of the natural history of the disease and without sacrifice of the patient's time or society's resources. Once diagnosis and clinical stage are determined, operation should be offered to those who are potentially resectable and radiotherapy and chemotherapy considered in those who are not.

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Continued on Page 277



Issues in Physician Recruitment to Rural Areas

David Kibbe, M.D.*

The Problem

One aspect of the health-crisis in the United States is the disparity between health needs and physician availability in rural areas of the country. There is a higher proportion of people with chronic disabling disease living in rural farm areas than anywhere else in the nation and a greater number of home bound disability days suffered per person per year in non-metropolitan areas.[1] Yet in 1971 143 counties in the U.S. had no active nonfederal physician, and many others had ratios of less than 25 physicians per 100,000 compared with 143 per 100,000 for the nation as a whole.[2] While the view that merely increasing the number of doctors who serve in rural areas will solve all the health needs of our rural population is no doubt over-simplified, it is obvious that physicians are unequally distributed among the nation's populace, and reasonable to believe that the shortage of physicians in rural areas is one cause of the lack of adequate health care services in rural regions. Various strategies to increase health benefits received by rural Americans are unlikely to change the current situation unless they include some means of influencing physicians to practice in rural sites. As one observer puts it: "All the national health insurance in the world will not buy health for a rural American who has no doctor to go to."[3]

Why do doctors generally choose to practice in non-rural areas? A number of sociological studies have addressed this question and used their findings to support suggestions regarding ways to encourage physicians to enter and stay in shortage areas.

Several papers have pointed out, and one in particular by Rushing, et al has documented, that the unequal distribution of physicians in the U.S. is part of a general tendency among all professional groups to settle in metropolitan regions, and that the frequent finding of an association between physician ratio and levels of wealth and urbanization in a population is "one aspect of a macrosocioeconomic process tending to favor those communities which have more social and economic advantages."[4] Rushing claims that physicians can be looked at as units of a highly organized service industry who are quite naturally attracted to the "external economies" of universities, research institutes, and access to large patient populations in areas of high population concentration. It seems hardly surprising that physicians tend to act in a fashion similar to other highly trained professional groups, but helpful to recognize because it may spell doom to certain programs aimed at redistributing physicians that do not take account of the trend. For example, if physicians continue to pattern their practice site decisions as they have in the past, the impact which increasing the absolute number of medical graduates is hoped to have on physician redistribution may simply be nullified, and the relative difference between advantaged and disadvantaged communities will continue or perhaps increase.

A host of dependent and independent variables have been examined in an effort to describe more clearly the factors affecting physician location. Practice in urban areas is associated with graduation from urban medical schools, and with graduation from certain medical schools.[1] Practice in rural areas has been found to be correlated with rural background, and a town's ability to attract new physicians correlates positively with the mobility and educational level of the population, and negatively with the percentage of the population involved in agriculture.[1] The number of specialists in an area, as another example, correlates with the education level of the population, the number of hospital beds per thousand persons, the presence of a medical school in the community, and the number of supportive institutions.[1] These and other associations are purely descriptive data which have only a limited usefulness in analyses of how to affect a change in physician distribution. They provide us with information about patterns of health-manpower distribution, but do not give us insight into the cause and effect relationships of these patterns.

Finally, some authors have looked prospectively and retrospectively at the personal biases, prejudices, and desires which have influenced physicians' decisions about rural practice. Although a variety of methods and questionnaire types have been employed on several physician groups, including those about to enter rural practice, physicians who have established rural practices, and doctors about to leave rural counties, certain attitudes do stand out. Physicians who are entering rural communities to practice emphasize the importance in their decision-making process of family background, a good community hospital, a nearby medical center, and other factors having to do with good professional support, such as the opportunity to join in a group practice, while those who choose not to practice in rural communities fear that by doing so they will lose the collegial support derived from practicing near a large medical center. These physicians also indicate that their decision to locate in an urban area was influenced by colleagues and professors during training.[4] Physicians who have left rural practice have mentioned as outstanding reasons that they felt the opportunities for professional growth were limited in their community, that the private practice of

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medicine in the area was a "dead end job", and that they were unable to rely on the physicians in that medical community for professional support.[3] The crucial importance of professional association and support is a theme which appears at the top of the list for all groups in the studies. It can probably be considered the chief factor determining perception of professional satisfaction when such support exists in a rural setting, and as a powerful negative influence when such support is absent or perceived to be lacking.

The Solutions

Some investigators interpret this finding to mean that health authorities, i.e., state and local agencies, the federal government, and universities and medical schools, should be able to increase the attractiveness of rural practice by instituting various programs designed to improve the professional support systems available to rural doctors. Among the plans proposed are continuing education and development programs, tax incentives to group practices in rural areas, and medical school involvement to connect the rural physician with the clinical resources of the large medical centers. Although I think that these strategies are valuable in their own right and may be effective measures to help shift the distribution of physicians if undertaken vigorously, I am sure the cost will be very high. And, I am forced to question the logic behind plans which seek to make rural medical environments more closely approximate the urban medical setting, especially when the rationale for doing so is not that the proposed professional support programs will directly improve health care in disadvantaged areas, but instead that this is what physicians seem to require in order to move out of the population centers. Since the focus of attention has fallen primarily upon physicians' prejudices and desires once these are already established, planning suggestions have gone to curiously great lengths to devise redistribution plans which would make rural living more satisfying to physicians. It is no less important to consider the factors which *shape* doctors' biases, and to investigate measures which would influence physicians to find satisfaction in serving in less than "perfect" professional environments, but in situations more realistically in line with the country's need for rural health care.

It is interesting to note that first year medical students tend to be quite undecided and non-committal on the issue of where to practice medicine when they eventually finish training,[6] and that physicians generally delay their decision on practice location until the residency period, or rather late in their training experiences.[1] These data substantiate what every physician is aware of, that medical school and graduate training experiences play an important role in shaping one's decision as to where to practice. Furthermore, they indicate that the medical school environment may be the crucible in which key professional attitudes and goals are forged. That these attitudes and goals have an impact on one's decisions about the benefits/disadvantages of practicing medicine in various locales and under certain sets of circumstances almost goes without saying, and implies that we ought to begin to evaluate the influences in the training environment which condition physicians to prefer the close professional and clinical support available in urban centers.

The conditioning process originates with the physical environment of most medical school campuses, the majority being located in large metropolitan areas where a mix of manpower training resources, including research facilities, libraries, specialty teaching faculties and large patient populations can be attained most easily and naturally. In the first phase of medical education, the pre-clinical lecture and laboratory period lasting from one to two years, medical students spend a large part of each day together, effectively isolated from other social and professional groups. Concentrated twelve hour study days six days a week for several months at a time are not uncommon. Community involvement, by which is meant activity shared by members of a socially-linked but professionally diverse group of persons with common goals and interests in an historical community is often severely restricted to medical students (and later, to interns and residents) by the demands of their educational environment. The "medical community" very early on becomes a surrogate for other types of social interaction which the student may have participated in at an earlier time. One adapts to this situation or one risks the penalty of falling behind in the intense course of study. Eager, enthusiastic to learn, and impressed with a sense of dedicated earnestness at having just (and finally!) crossed the threshold of the profession of Medicine, most beginning medical students readily accept the sacrifice of their broader social interests without questioning very thoroughly the patterns of professional behavior that are being set.

The tendency towards dependence on the medical community for satisfying professional goals intensifies as training proceeds into the clinics and wards of a large medical center. The tertiary care center is a unique environment devoted to education, or as Dr. Eugene Stead of Duke has written, "Medical schools and their closely affiliated hospitals form medical centers that have as their primary purpose the conversion of untrained manpower into trained manpower...the community hospital is a place where physicians give services to people."[5] Despite the depth of specialized knowledge available for educational purposes in a medical center, the environment there is quite narrow insofar as the principal educators are highly trained specialists whose careers have been confined to working within an academic center and whose interests are in treating patients acutely ill or suffering from relatively rare chronic disease and who have been referred from secondary hospitals for specialized care. Clerkships, being mainly hospital-based, involve hospitalized patients

on whom the original screening and decision-making have already been completed. Students do not see patients in the office, at home, in the community at work, or in nursing homes. In effect, they see both medical practice and patients from the specialists' point of view. The role models from whom so much about medical practice as well as about illness and disease must be learned are men and women who require the research, technological, and specialized staff capabilities of the medical center to practice in their fields of interest. In this era when board certification in any of the major specialties requires a minimum of three years of postgraduate training, it is really any wonder why physicians who have spent seven to ten years working and training in medical centers come to the completion of their education less than eager to move outside the medical center's sphere of influence to practice?

Finally, such considerations as financing, scheduling, staffing, and planning for personal and family needs necessary for the management of a medical practice are not included in the traditional training of most physicians. The lack of experience with the practical aspects of establishing and operating a medical practice may be one reason why physicians feel most comfortable remaining in close contact with medical schools, clinical centers, and professional institutions that offer these important ancillary services.

In conclusion, the problems involved in redistributing physicians more equally among urban and rural populations demands more than the attempt to lure doctors away from the cities via professional support systems. What is also required are basic reforms in the medical education process that will prepare a segment of the doctors in training for the more independent professional life style needed for rural practice, and that will encourage them during training to take a broader perspective of the medical professional's role in a diverse society.

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A Preliminary Analysis of Surgical Trends in Maine: 1974-1975

Ellen M. Naor* and Alice M. Russell**

Introduction

The largest single category of expenditures for health care in Maine in 1974 and 1975 was that of hospital services. In 1975, an estimated 41% of all health care expenditures in Maine were for hospital care. It is estimated that $202 per capita were spent of hospital services in that year.[1] The use of surgical procedures represents one of the most important and expensive components of hospital care. Of 156,802 total admissions to Maine hospitals in 1975, 43.3% were for surgery, which accounted for 45.4% of total patient days. Maine data show the cost per day to be 33% higher for surgical than for non-surgical cases.[2] The result is that hospitalizations involving surgical procedures account for half of all hospitalization costs. Studies of surgical practice, therefore may have important implications for cost containment programs administered by health planning agencies, third party payors, PSRO's, and other professional groups.

In 1973, Wennberg and Gittelsohn described in *The Journal of the Maine Medical Association* a population-based method of studying health care delivery. They recommended the use of population-based health information systems in planning and decision-making in the health care field.[3,4,5] They demonstrated the unique utility of population-based measures for identifying those variations in health services utilization which cannot reasonably be attributed to differences in illness rates of the population studied. They hypothesized that one explanation for the variations in utilization identified by this method might be the uncertainty which exists among physicians regarding the necessity for and effectiveness of different approaches and/or procedures for patient care. Wennberg and Gittelsohn argued that analyses of population-based data for small areas would provide a more rational basis for decision-making in the health care field. Such data can provide PSRO's and third party payors with a means for measuring the wide variations in the level of services among residents of different communities. The utility of these methods in determining the existence and magnitude of unnecessary surgery has been studied by the National Professional Standards Review Council.[4]

The population-based method has been used to study the utilization of surgical services in Maine. The studies documented the existence of wide variations in surgical rates among geographically defined populations. The use of population-based measures in that study introduced a comparative dimension which was not possible with institution-based data as previously used. Areas of similar population size, geographic location, and socio-economic characteristics differed markedly in their residents' rates of hospitalization; rates for specific surgical procedures varied even more widely.

This study does not address these geographical variations in the incidence of surgery throughout Maine. Rather, the purpose of the present study is to expand on these initial analyses by examining trends in surgical use rates from 1974 to 1975, using the population-based approach. The following questions are explored in this paper: Was there a significant change in the incidence of surgery state-wide? Did all hospital service areas experience similar changes? Was there a difference among procedures in any changes experienced? Were the same procedures responsible for changes in the various service areas? The preliminary findings of an analytic approach focused on these questions are reported here.

Methods and Materials

The data on which this study is based are produced from computerized hospital discharge records maintained by the Maine Health Data Service (MHDS) and the Professional Activity Study(PAS); together these two sources cover all discharges from Maine short-term general hospitals. Since 1973, these two files have been merged annually and combined with population estimates to obtain age- and sex-specific inpatient hospital use rates by diagnosis and principal surgical procedure for specified geographic areas.[7]

Two years, 1974 and 1975, were selected for a preliminary study to demonstrate an organized and rational method for assessing trends in the use of surgical procedures and to evaluate its utility in detecting and describing changes in the incidence and distribution of surgical procedures in Maine. Excluded from the surgical use rates considered in this analysis are the following: biopsy, diagnostic endoscopy, radiography, radiotherapy, other operations inducing or assisting delivery, or any other non-surgical procedures.

Hospital service areas have been established in Maine on the basis of patient origin studies; each town is assigned to the hospital receiving the plurality of admissions of that town's residents. Surgical use rates were calculated for residents of forty hospital

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service areas; two additional service areas (accounting for 2.5% of Maine's population) were excluded from this study because accurate service area population figures are not available. This analysis is population-based rather than institution-based. The rates show hospital use for surgery by area residents regardless of where hospitalization took place, thus accounting for the effect of referrals in and out of areas. For example, if a patient from the Brunswick area is admitted to a Portland hospital, his admission is credited back to the Brunswick population.

The rates were adjusted to reflect the specific age structures of each service area's population. By removing the effect of varying age distributions, the resulting surgery incidence rates allow accurate, unbiased comparisons of areas to be made. Age-adjusted rates, using the total Maine population as the standard for each year, were used in all geographic comparisons.

For this study, ten frequently performed surgical procedures,* which represent one-third of all inpatient surgical cases in Maine, were studied in detail: tonsillectomy and adenoidectomy, dilation and curettage of the uterus, hysterectomy, inguinal hernia repair, cholecystectomy, appendectomy, mastectomy, prostatectomy, hemorrhoidectomy, and excision and ligation of varicose veins.

Analysis of the specific use rates for each of these ten procedures by hospital service area was limited to the 26 service areas with populations of more than 10,000 persons, since some of the frequencies of individual procedures in the smaller areas were too small for meaningful statistical analysis. That is, analysis of total surgical incidence by service area was based on the entire group of 40 areas, while analysis of individual procedures by service area was limited to the 26 areas with populations greater than 10,000 persons.

Changes in surgical incidence from 1974 to 1975 were assessed using a normal approximation to evaluate differences between observed and expected frequencies. The expected frequencies of surgery in 1975 were calculated by applying age-specific 1974 rates for each procedure to the 1975 population estimates. In the following tables, statistical significance at the 99.9% confidence level ($p < .001$) is indicated by ***. The high significance level was selected as a conservative measure since a large number of tests were performed in the course of the analysis and because only two data points (i.e., two years of data) were studied.

Results

From 1974 to 1975, the overall number of inpatient surgical procedures decreased by 1,505 cases (2.2%) from 69,333 to 67,828. As shown in Table 1, the 40 hospital service areas studied experienced varying

*Only cases which recorded these procedures as principal were included in the analyses.

Continued on Page 273

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WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. *Drug Dependence*: Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy*: Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children*: Tenuate is not recommended for use in children under 12 years of age.
PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.
ADVERSE REACTIONS: *Cardiovascular*: Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System*: Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal*: Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic*: Urticaria, rash, ecchymosis, erythema. *Endocrine*: Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System*: Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous*: A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.
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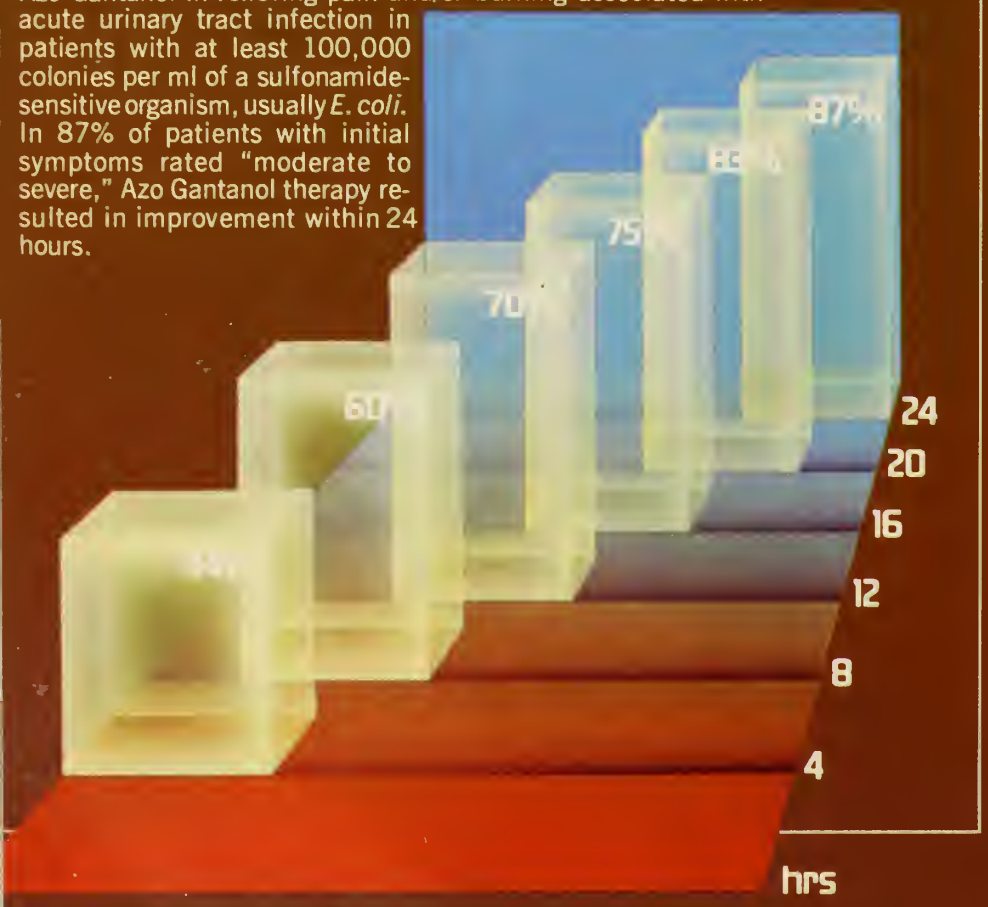
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TABLE 1

INCIDENCE OF SURGERY BY HOSPITAL SERVICE AREA
MAINE, 1974-1975

Hospital Service Area[a]	Number of Procedures Performed 1974	1975	% Change	Rates per 1,000 Population[b] 1974	1975	% Change	Statistical Significance[c]
TOTAL	69,333	67,828	− 2.2	72.2	66.3	− 8.2	***
1	364	400	+ 9.9	59.1	61.9	+ 4.7	
2	4,761	4,830	+ .1	73.8	74.0	+ .3	
3	88	94	+ 6.8	72.3	76.8	+ 6.2	
4	5,968	6,314	+ 5.8	56.8	59.5	+ 4.8	***
5	936	1,014	+ 8.3	89.0	96.1	+ 8.0	
6	437	448	+ 2.5	51.9	49.0	− 5.6	
7	44	45	+ 2.3	45.8	43.5	− 5.0	
8	836	891	+ .7	56.3	57.6	+ 2.3	
9	755	875	+15.9	51.1	57.9	+13.3	***
10	255	299	+17.2	58.9	68.4	+16.1	
11	1,101	1,226	+11.3	87.2	96.0	+10.1	***
12	969	1,057	+ 9.1	57.1	63.7	+11.6	
13	916	1,008	+10.0	57.8	63.8	+10.4	
14	267	269	+ .7	57.6	57.1	− .9	
15	367	436	+18.8	83.4	100.1	+20.0	***
16	506	506	0	57.3	56.8	− .9	
17	1,318	1,290	− 2.1	74.1	71.2	− 3.9	
18	857	807	− 5.8	64.4	59.6	− 7.5	
19	3,244	2,942	− 9.3	65.2	58.6	−10.1	***
20	507	505	− .4	89.1	88.4	− .8	
21	734	720	− 1.9	70.5	67.3	− 4.5	
22	2,214	2,134	− 3.6	66.5	62.9	− 5.4	
23	351	326	− 7.1	48.8	44.9	− 8.0	
24	13,194	12,375	− 6.2	73.8	68.5	− 7.2	***
25	1,760	1,719	− 2.3	56.1	54.1	− 3.6	
26	1,277	1,229	− 3.7	55.9	53.0	− 5.2	
27	1,447	1,305	− 9.8	63.2	56.0	− 5.2	***
28	6,833	6,714	− 1.7	69.5	67.9	− 2.3	
29	932	886	− 4.9	76.5	71.5	− 6.5	
30	1,857	1,701	−10.9	77.1	71.0	− 7.9	***
31	979	898	− 8.3	82.7	75.0	− 9.3	
32	1,978	1,940	− 1.9	77.8	75.5	− 3.0	
33	5,164	4,751	− 8.0	95.2	86.6	− 9.0	***
34	634	596	− 6.0	65.3	69.8	− 8.4	
35	524	500	− 4.6	70.8	66.7	− 5.8	
36	215	197	− 8.4	74.5	65.6	−11.9	
37	300	272	− 9.3	105.3	94.3	−10.4	
38	833	733	−12.0	69.7	60.7	−12.9	***
39	710	697	− 1.8	62.1	61.2	− 1.4	
40	1,855	1,839	− .5	74.2	73.1	− 1.5	

a Hospital service area numbers represent the same area throughout this analysis.
b Age-adjusted rates per 1,000 population.
c Statistically significant changes in use rates are indicated by *** ($p < .001$).

changes in surgical use rates ranging from the 20% increase in Area 15 to a 13% decrease in Area 13. The aggregate change in the 28 areas which experienced decreases in inpatient surgery was substantially greater than that in areas of increase, resulting in the overall net decrease. The extent to which such changes represent true, underlying changes in surgical practice rather than random fluctuation or changes in population structure was assessed by statistical comparisons using population-based rates, as outlined above. Thus, ten of the 40 hospital service areas studied experienced statistically significant changes ($p < .001$) in the incidence of surgical procedures between these years. Significant decreases were observed in six service areas, while significant increases occurred in four areas. Statewide, the overall reduction in surgical use rate from 72.2 per 1,000 to 66.3 was statistically significant as well ($p < .001$).

The data on the principal procedure performed were then studied to determine whether these changes were due to the use rates of specific procedures or rather reflected overall reductions. Investigation of trends by type of procedure was limited to ten selected procedures as noted above. These are shown in Table 2, together with the number of cases and use rates for each procedure.

The significant overall decrease in the incidence of

TABLE 2

INCIDENCE OF TEN SELECTED SURGICAL PROCEDURES
MAINE, 1974-1975

Procedure	Number performed 1974	1975	% Change	Rates per 1,000 Population 1974	1975	% Change	Statistical Significance[a]
T & A	5,357	3,980	−25.7	5.6	3.9	−30.4	***
D & C[b]	4,612	4,012	−13.0	4.8	3.9	−18.8	***
Hysterectomy[b]	2,810	2,905	+ 3.4	2.9	2.8	− 3.4	
Hernia repair	2,403	2,440	+ 1.5	2.5	2.4	− 0.04	
Cholecystectomy	2,215	2,354	+ 6.3	2.3	2.3	− 0	
Appendectomy	1,532	1,595	+ 4.1	1.6	1.6	0	
Mastectomy	1,481	1,642	+10.9	1.5	1.6	+ 6.7	
Prostatectomy[c]	1,287	1,280	− 0.5	1.3	1.2	− 7.6	
Hemorrhoidectomy	559	610	+ 9.1	.6	.6	0	
Varicose Veins	508	475	− 6.5	.5	.5	0	
Selected procedures	22,764	21,293	− 6.5	23.7	20.8	−12.2	***
All Others	46,569	46,535	− 0.1	48.5	45.5	− 6.2	
TOTAL	69,333	67,828	− 2.2	72.2	66.3	− 8.2	***

a Statistically significant changes in statewide use rates are indicated by *** ($p<.001$).
b Rates based on female population only.
c Rates based on male population only.

inpatient surgical procedures was principally accounted for by decreases in the numbers and rates of tonsillectomy and adenoidectomy (T&A) procedures and dilation and curettage procedures (D&C) (Table 2). The other eight procedures studied in detail actually increased somewhat in number.

Specifically, the number of T&A's performed decreased 26% between 1974 and 1975, corresponding to a rate decrease of 30%. Statistical analysis based on the population distribution, i.e., on the age-adjusted rates, showed the decrease to be highly significant ($p<.001$). The number of D&C procedures also decreased markedly, by 13%. This corresponded to a decrease of 19% in the rate, which was significant statistically ($p<.001$).

These two procedures, T&A and D&C, were those performed most frequently in both 1974 and 1975, hence the significant decreases in their use rates resulted in statistically significant decreases in both the overall State rate and the use rate for the group of ten selected procedures. On the other hand, the use rate for the residual group of all other procedures was virtually constant between 1974 and 1975. This does not mean that the frequencies for individual procedures in the "all other" group necessarily remained unchanged, however.

These findings suggest that the interrelationships between changes in overall area use rates and changes in the incidence of specific procedures be examined. Table 3 offers some insight into the variations of the ten selected surgical procedures, from 1974 to 1975, in the 26 hospital service areas with populations of more than 10,000 persons. This table details the occurrence and statistical significance of changes in the incidence of each procedure for each area. There was

TABLE 3

CHANGES IN INCIDENCE OF TEN SELECTED SURGICAL PROCEDURES FOR LARGE HOSPITAL SERVICE AREAS[a]
MAINE, 1974-1975

Procedure	Statistical Significance Statewide[b]	Areas with Significant Increases[c]	Areas with Significant Decreases[c]
T&A	***	25	2,4,12,22,24, 27,28,32,33
D&C	***	12	2,24,27,33
Hysterectomy		18	19
Hernia repair		4	
Cholecystectomy		4,12	
Appendectomy		4	
Mastectomy		4,28	
Prostatectomy		8,9	19
Hemorrhoidectomy		5,8,38	
Varicose Veins		12	

a Code numbers representing hospital service areas with populations o more than 10,000 persons.
b Statistically significant changes in statewide use rates (from Table 2 are indicated by *** ($p<.001$).
c Code numbers representing hospital service areas whose use rates fo the procedure changed significantly ($p<.001$) between 1974 and 1975.

considerable variation among the areas in the number, type of procedure, and direction of changes in surgical use rates. Significant changes in one or two areas in the use rate for a specific procedure were not generally reflected in corresponding Statewide changes for that procedure. However, this table paradoxically suggests the existence of underlying patterns of variation as well; these are summarized in Table 4.

Thus, for most surgical procedures studied, the

TABLE 4

SUMMARY OF CHANGES IN INCIDENCE OF TEN SELECTED SURGICAL PROCEDURES FOR LARGE HOSPITAL SERVICE AREAS[a]

Procedure	*Statistical Significance Statewide*[b]	*#areas with no significant change*	*# areas with significant increases*[c]	*#areas with significant decreases*[c]
T&A	***	16	1	9
D&C	***	21	1	4
Hysterectomy		24	1	1
Hernia repair		25	1	—
Cholecystectomy		24	2	—
Appendectomy		25	1	—
Mastectomy		24	2	—
Prostatectomy		23	2	1
Hemorrhoidectomy		23	3	—
Varicose Veins		25	1	—

a Hospital service areas with populations of more than 10,000 persons.
b Statistically significant changes in statewide use rates (from Table 2) are indicated by *** ($p<.001$).
c Hospital service areas whose use rates for this procedure changed significantly ($p<.001$) between 1974 and 1975.

majority of service areas did not exhibit significant changes in the incidence of the procedure (Table 4). In other words, high incidence areas remained high, and low use areas remained low. One notable exception, of course, was the incidence of T&A procedures; statistically significant decreases were found in nine of the 26 service areas studied. In the case of D&C procedures, on the other hand, only four areas experienced significant decreases but these were large enough to result in a significant statewide decrease for this procedure.

DISCUSSION

The results of this study must be interpreted with some caution since only two years of data have been considered. It is possible that some or all of the changes noted in service areas will not recur in other years. Conversely, more subtle trends may exist which cannot be detected until data for four or five years are compiled and analyzed. This analysis was undertaken as a pilot study of the appropriateness and utility of the approach; discussions of the initial findings as reported here have suggested a number of factors whose contributions to the observed variations will be examined further.

For example, the significant decreases in the use rates for T&A procedures might be associated with compensatory increases in other related procedures such as adenoidectomy (alone)[8] or other otolaryngological procedures which are singly not frequent enough to provide a basis for statistical evaluation but jointly might constitute a "replacement phenomenon" with regard to this procedure. Of course, increasing use of outpatient procedures in place of T&A surgery would not fall in this category. Consideration of the specific areas responsible for the reduction in T&A use rates show them for the most part to be urbanized areas with major medical centers.

With regard to D&C use rates, it seems possible that some of the decrease in the incidence of this procedure may reflect increasing performance of D&C's on an outpatient basis. In addition, there may be changes in the reporting conventions regarding abortions as well as in the increasing use of outpatient facilities for abortions. The major reductions in the procedure occurred in areas with large hospitals.

Further speculation regarding the occurrence of replacement phenomena points to the need for more detailed analysis of the residual group of "all other procedures" which constituted approximately two-thirds of all procedures performed. By spotlighting ten frequent procedures, this analysis has in effect overlooked changes which might be occurring in the residual group. Although most individual procedures in this group have low use rates, it will be important to find ways to analyze the differences in case mix, perhaps using groups of procedures rather than individual procedures, and to extend the analysis over several years to detect changes in the frequencies and rankings of the various procedures.

Other factors which may contribute to the observed changes in use rate are the levels of physician/surgeon manpower resources in various areas, the distribution of surgeons with specific specialties, the availability of hospital beds, the existence and availability of technical diagnostic and treatment equipment, and the reimbursement policies of the various third party payors. Such related studies are presently underway, utilizing data from Cooperative Health Statistics System components as well as further in-depth and trend analyses of the hospital utilization data. Preliminary review of 1976 surgical data being currently analyzed confirms the trends observed between 1974 and 1975.

If these limitations are kept in mind, the

preliminary results of this study can be useful in suggesting and testing the utility of the approach for measuring physician activity in the area of surgery, formulating new physician programs, developing health plans and policies, and evaluating certificate of need applications. This experience, in turn, will feed back into the continuing analyses of these data and enhance their relevance to ongoing efforts to improve the quality, efficiency, and effectiveness of hospital care.

Several illustrations of the current use of trends analysis in conjunction with other data on hospital use and resource availability follow:

Health Planning: Continuing study of trends in surgical practice is essential in developing rational plans for the provision of acute care services and recommending appropriate goals for the rate of surgery in the State. The format adopted by the (Maine) State Health Coordinating Council for the State Health Plan and the Health Systems Plan requires population-based planning, as does P.L. 93-641 itself; proposed strategies must be quantified and measurable, insofar as possible. Analyses of surgical trends will thus constitute an essential element of relevant plan components. It is anticipated that the State Medical Facilities Plan now being developed will be heavily based on consideration of trends in hospital use and surgical practice.

Resource Development: When a hospital is considering expansion (or reduction) of beds or addition (or deletion) of services, the trend in use rates in that hospital's area relative to those in other areas and to the State average is useful in evaluating the number of beds and services which may be needed. Analyses of trends in surgical practice have proved to be an important complement to studies of overall hospital use in this regard and have served as a focal point for discussions of multi-institutional sharing agreements or regionalization of services.

Second-opinion Surgery Programs: One county medical society in Maine recently implemented a county-wide program to provide a second opinion (at no charge) regarding surgery need, for a six-month trial period. Maine Blue Cross implemented a Statewide second-opinion program on January 1, 1979, in which Blue Cross will pay for the second opinion. Blue Cross will use this study to identify existing patterns of variation, suggesting areas most likely to respond to program implementation with significant changes. This study will provide baseline data against which the subsequent incidence of surgery will be compared as part of the monitoring and evaluation of the second opinion program. Maine's PSRO has just implemented a "hot line" program which will provide the names of specialists for second-opinion purposes. Again, these data will provide a source of baseline data for monitoring program effectiveness.

PSRO/Focused Review: Maine's Statewide PSRO is presently formulating an overall plan for "focused review" which would identify those surgical procedures and hospital service areas which consistently remain within an average range to the Statewide average and the procedures and hospital service areas which exhibit a more substantial variance. More efficient review will result by discontinuing 100% review on cases which do not vary from the Statewide average and intensifying review of cases which vary substantially.

The PSRO is funding an analysis of the 100% acute care data base as part of this project. The results of this analysis will be used as input to the PSRO focused review plan.[9]

Continuing Education Programs: The Continuing Education Committee of the Maine Medical Association is presently exploring the utility of studies of surgical variations and trends as indicators for physician education programs, suggesting possible target areas for specific programs on a regional as well as Statewide basis. The studies in themselves will also serve as effective educational tools. Ultimately, trend studies will provide bases for evaluating the impact of such programs. Presentations of surgical trends data have also been effective in demonstrating the need for health care personnel from various disciplines to focus on small area variations, using population-based methodologies.

Summary

This preliminary study found an overall decrease of 2.2% in inpatient surgical procedures between 1974 and 1975. Most of the reduction was accounted for by two procedures, and the decrease occurred primarily in certain hospital service areas. In other words, most procedures studied and the majority of service areas remained constant in the incidence of surgery from one year to the next: high incidence areas remained high and low incidence areas, low.

—Six hospital service areas experienced statistically significant decreases in their overall use rates for total surgical procedures between 1974 and 1975, while four areas had significant increases.

—Thirty of the 40 hospital service areas did not experience significant changes in the overall incidence of surgical procedures.

—The rate of T&A procedures performed decreased by 30%; significant decreases were observed in nine of the 26 service areas studied.

—The rate of D&C procedures decreased by 19% Statewide; significant decreases were observed in four of the 26 service areas studied.

—All of the other eight procedures studied experienced less than 10% change from 1974 to 1975 and none were statistically significant.

Extension of this study is essential in order to determine the stability of such trends over a several year period, to identify concomitant patterns of change in related variables such as physician man-

power and available facilities, to determine whether or not significant decreases in specific procedures are associated with compensatory increases in others, to changes in the many procedures not included in this analysis, and to assess associations of surgical use rates with hospital costs.

Results of the preliminary analysis are already being used in a variety of applications. In development of health plans and the State Medical Facilities Plan, certificate of need determinations, and manpower assessment, comparisons of trends in a specific area relative to those of other areas and the State as a whole are useful in determining the number of beds and services needed and the adequacy of existing manpower and facility resources. Analysis of surgical trends has been incorporated into programs for assessing the quality of care rendered, developing continuing education programs, and evaluating responsiveness to changing service delivery patterns. This initial study underscores the importance of basing assessment and projection of surgical trends on small geographic areas, since there is substantial variation among them in both the magnitude and change in consumption of services.

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Meeting Dates for Your Calendar...

AMA House of Delegates Interim Meeting

Honolulu, Dec. 2-5, 1979

Winter Scientific Meeting

San Antonio, Jan. 12-15, 1980

ABSTRACTS
Fifth Annual Maine Biomedical Science Symposium
The University of Maine at Orono
June 14-15, 1979

ALCOHOLISM

Overview of Alcohol and Drug Education Project

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The current work of the Unit for Alcohol and Drug Education, including the Student-Teacher-Parent Alcohol and Other Drug Project, will be overviewed.

The nature and progressive development of chemical dependency will be described and related to prevention education and intervention strategies.

Ethanol Consumption in Genetically Selected Hypertensive and Hypotensive Mice

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The purpose of this study was to examine the relationship between blood pressure level and ethanol consumption in genetically selected hypertensive and hypotensive mice. The design permitted an evaluation of whether there was a causal relationship between blood pressure phenotype and ethanol consumption. In addition, the effect of age on ethanol consumption was studied. Hypertensive mice consumed significantly more ethanol solution than did the hypotensive mice. Results indicated that this relationship was not causal; F_2 hypertensive and hypotensive mice did not differ in amount of ethanol consumed. Age did not influence ethanol consumption. The results indicate that genetic tests should be performed to determine whether relationships between blood pressure phenotype and ethanol consumption reflect causal relationships (direct or indirect) or mere artifacts of selection.

Alcohol and Aging

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Alcoholism is a serious problem for elderly individuals. This is an area that has received little attention both clinically and with regard to research. It is suggested that the criteria used for diagnosing alcoholism may be confounded with changes associated with aging. Moreover, there would appear to be two types of elderly alcoholics: the chronic alcoholic who has had a drinking problem for several years and the situational alcoholic who abuses alcohol in response to the physiological and behavioral changes sometimes associated with aging. Methods for identifying the elderly alcoholic are discussed. In addition, future directions for research are presented, e.g., the development of an animal model of aging and alcoholism.

Alcohol and Women: Physiological and Behavioral Effects

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Recent evidence suggests that many of the psychological and physiological effects of alcohol on women may be related to unique female characteristics; e.g., changes in female sex hormonal conditions as reflected by the phase of the menstrual cycle, use of oral contraceptives, pregnancy, hysterectomy, menopause, and estrogen replacement therapy. The development of physiological and behavioral tolerance to alcohol in women may be related to these hormonal conditions that occur at different stages in the life span of the individual. A tentative and hypothetical model of alcohol addiction in women will be presented that suggests that there may be a relationship of sex hormonal status to depression. This condition may result in alcohol being self- administered to reduce the psychological and physiological concomitants of depression. However, as the sex hormone status changes with age more alcohol may be required to produce similar behavioral effects and finally cognitive deficits may begin to appear as subtle brain changes develop. Neuropsychological studies suggest that cognitive deficits in women may be related to the status of sex hormonal levels when they begin to drink excessively. Future research should be directed toward integrating the social, cultural, biological, and psychological factors related to the effects of alcohol on women.

BEHAVIOR AND LIFE SPAN DEVELOPMENT

Sex-typed Play with Boys' and Girls' Toys

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Two studies investigated the relationship between the use of boys' or girls' toys, and the presence of sex-typed characteristics in children's play. In a free-choice situation, 30 4th - 6th grade boys and girls built play constructions and told descriptive stories using blocks, dolls, doll furniture, animals and vehicles. Although only girls showed strong sex-typed toy preferences, correlational analysis established strong relationships between the selection and use of certain sex-typed toys, and the presence of masculine or feminine characteristics in the play constructions and stories.

In order to determine the relationship between sex-typed toys and sex-typed play in the absence of differential toy preferences, a second study limited the children's choice to blocks (a neutral toy, according to the first study), and either boys' or girls' toys. Twenty-two boys and 22 girls made play constructions and told stories using either blocks and vehicles, or blocks, dolls and doll furniture. Results showed that girls and boys built masculine constructions and told masculine stories with boys' toys, but built feminine constructions and told feminine stories with girls' toys. In conclusion, selection of gender-appropriate toys in free play situations may result in masculine play by boys and feminine play by girls, masking the children's facility for cross-gender play when other toys are selected.

Affective Responses to Early Motherhood

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The transition to parenthood is one of the most significant adult life changes, particularly for women. Yet little is known about the affective and experiential qualities of the early phase of mothering.

In this paper, we briefly review the development of thinking and empirical findings on early motherhood, and report on our recent study of the experiences of parents with young first children. Our emphasis is on understanding the meaning mothers give to their parenthood. We suggest that this process of meaning construction is organized around a set of thematics. These themes can be seen as representing a personal myth structure, a saga by which the mother's past, present and future take on both coherence and elements of heroic striving. The terms of this myth structure, and the ways that motherhood reinforces or undermines it, are intimately tied to the parent's affective responses to the child and the life stage. This mythology incorporates not only the mother's sense of self, but also her experiential map of the external world as revealed in her actions, definitions, beliefs, perceptions and fantasies. The mythology represents an entire definitional structure through which the mother attempts to order her experience.

The attempt to maintain this structure in the face of a chaotic and sometimes contradictory reality often forces her into extreme efforts at editing and denying input, to live as if the connection between things and their potentialities were not ruled by deterministic processes, but by magic.

Application of Tests for Physiologic Age

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Physiological tests of age could help determine the biological age of an animal as well as find which organ or tissue systems contribute most toward the decline in function causing death. Each test must show a significant decline in function over the lifespan of the animal. The test must also be repeatable within an animal for longitudinal studies. We would like to show similarities in the aging rates in some of the different organ and tissue systems as well as predict lifespans of animals with different physiological aging rates. The tail collagen physiological test is used as a possible example of a physiological test of age.

Serotonergic-catecholaminergic Antagonism and Locomotor Control

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Scottish Terrier dogs afflicted with a quantifiable locomotor defect exhibited a dramatic decrease in serotonin turnover concomitant to a skeletal muscle hypertonicity. The onset of hypertonicity was expedited by blockade of serotonin receptors with methysergide, confirming previous data suggesting that serotonergic neurotransmission is involved in locomotor control. The onset of hypertonicity was delayed by blockade of alpha catecholamine receptors with phentolamine or phenoxybenzamine-HCl. Phenoxybenzamine-HCl not only delayed the onset of hypertonicity, but also prevented the decrease in serotonin turnover which accompanied the hypertonicity. Several locomotor defects in both canines and humans are accompanied by decreases in serotonin turnover, and may be counteracted by administation of serotonin precursors. Despite this, the data presented here suggest that the actual defect may not lie in the serotonergic neurons themselves, but may be due to an exaggerated antagonism by catecholaminergic neurons. (Supported by GM 07125-03).

Gene-environment Interaction: The Effect on Life Span in Inbred Mice

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Different strains of mice vary in their mean lifespan. The three genotypes to be discussed in this paper are representative of this variance, i.e., DBA/2J mice are shorter lived than C57Bl/6J mice which in turn are shorter lived than the F_1 hybrid (C57Bl/6J X DBA/2J F_1) mice. The mean lifespan of these genotypes has shown an increase during the last 20-25 years. This reported increase has been attributed to environmental factors, mainly improved husbandry. The important point, however, is that the increase has been constant across all three genotypes so that the mean order has remained unchanged. The current investigation was undertaken to determine whether environmental experiences, other than husbandry, had similar effects on lifespan in all three genotypes or if the same environments have differential effects. The results indicate that the life experiences of the genotypes affect mortality rate, but that the effects are constant so that the genotypes maintain their relative lifespan positions. Thus, within a genotype the contribution of the environment is an important factor in determining life expectancy, but such factors affect all genotypes equally.

Neurobehavioral Potentials in Development

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The development of visual electrocortical potentials (VEP) recorded from kittens and rat pups will be described and then discussed in terms of their differentiation by various parameters (waveform, topography, etc.) and experimental manipulations (lesions, anesthetics, etc.). This data will then be related to (a) visual behavioral development in these species, (b) similar VEP's obtained from premature human infants, and (c) relevance for future human infant neurobehavioral studies.

CELL AND MOLECULAR BIOLOGY

Effect of 25-Hydroxycholesterol on Dolichol and Sterol Synthesis in Mammalian Cell Cultures

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Dolichols are long chain polyisoprenoid alcohols found in many mammals and yeasts. Many enzymes are common to the pathways of both cholesterol and dolichol synthesis, in particular 3-hydroxy-3-methylglutaryl coenzyme A (HMC-CoA) reductase, which is a major regulatory enzyme for cholesterol biosynthesis. When 25-hydroxycholesterol, an inhibitor of HMG-CoA reductase in cultured cells, was added to L cell cultures, [^{14}C]acetate incorporation into both dolichol and sterol decreased in a concentration-dependent manner although the relationship between the concentration of 25-hydroxycholesterol and the level of inhibition differed for the two lipids. Situations may exist in which large fluctuations in sterol synthesis can occur while the rate of dolichol synthesis is only slightly affected. However, when sterol synthesis was repressed to levels below approximately 25% of the control level, further decrease in sterol synthesis was accompanied by a proportional decline in dolichol synthesis. The results suggest that HMG-CoA reductase affects the rate of dolichol synthesis by altering the concentrations of a substrate for the dolichol branch of the pathway, which is saturated at a lower concentration of substrate than is necessary to saturate the remaining cholesterol pathway past the branch point. The data therefore indicate an interaction by which two or more biosynthetic pathways can share common intermediates and a regulatory enzyme while maintaining a large degree of regulatory independence.

Mitogenicity of Modified Phytohemagglutinins

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Phytohemagglutinin isolated from *Phaseolus vulgaris* was modified by treatment with acetic anhydride, citraconic anhydride, glycinamide/carbodiimide, S-methylisothiourea, tetranitromethane, 2-hydroxy-5-nitrobenzyl bromide and N- bromosuccinimide and tested for ability to stimulate peripheral lymphocytes from 2 health human donors, *in vitro*. Acetylation of the lectin reduced mitogenicity. Citraconylation did not affect mitogenicity at low concentrations of lectin but higher concentrations brought a rapid decrease in thymidine uptake. Guanidated lectin was as mitogenic as unmodified phytohemagglutinin at low concentrations. At high concentrations, lymphocytes from one donor responded as well to the derivative, whereas the opposite was observed with other donor. Masking of carboxyl groups with glycinamide produced a less active mitogen. Modification of tryptophan residues by treatment with N-bromosuccinimide resulted in loss of mitogenicity. In contrast, the lectin was much less affected after reaction with 2-hydroxy-5-nitrobenzyl bromide. Nitration of phytohemagglutinin produced a lectin completely devoid of mitogenicity. Glycinamide-, homoarginine-, and nitrophytohemagglutinin remained tetrameric, whereas acetyl-, citraconyl- and N-bromosuccinimide-treated lectin were dimeric. Antinative lectin antiserum cross-reacted with all the modified proteins, except in the case of N-bromosuccinimide modification. The results show that the mitogenic property of phytohemagglutinin may depend on intact aspartic, glutamic and tyrosine residues but not lysine residues.

Cholesterol Synthesis in Chinese Hamster Cells Resistant to 25-Hydroxycholesterol

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Derivatives of cholesterol oxygenated in the 6,7 or 15 positions of the sterol nucleus or in the 20,22,24 or 25 positions of the sterol side chain as well as 32-hydroxylanosterol and serum lipoproteins were all shown to be potent inhibitors of sterol synthesis and 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in wild type Chinese hamster lung (Dede) fibroblasts. In contrast, sterol

synthesis and reductase activity in a clone of Dede cells which had been selected for resistance to growth inhibition by 25- hydroxycholesterol were resistant to the effects of all of the cholesterol derivatives, the lanosterol derivative and serum lipoproteins. The Km (HMG-CoA), thermal stability, and susceptibility to inhibition by Mg^{2+} and ATP of reductase activity were unaltered in the resistant clone. Rates of uptake and metabolism of 25- hydroxycholesterol did not differ between the resistant and wild type lines. Luria-Delbrück fluctuation analysis indicated that the occurrence of the resistant phenotype was a random event (variance = 74.1) occurring at a relatively low rate (3.4×10^{-7} mutations/cell/generation). The mutant clone retained phenotypic resistance to suppression of growth and sterol synthesis in the absence of 25-hydroxycholesterol.

Characterization of a Newly Developed Stable Line of Chick Cells

MARYANN JERKOFSKY and CHARLES E. BUCK, Dept. of Microbiology, University of Maine, Orono, ME 04469

At the present time, there is no established stable cell line of chicken origin. We have developed such a cell line from chick embryo cells. This stable cell line, which has undergone more than one hundred passages in our laboratory, maintains an epitheloid morphology. Chromosome studies demonstrate the typical chicken chromosome pattern with the presence of microchromosomes. Various immunological techniques have also been used to demonstrate that the cells are of chick origin. Antisera prepared against primary chick embryo fibroblast (CEF) cells killed the newly developed cells in a standard cytotoxicity test whereas the antisera did not kill human or monkey stable cell lines. The same antisera employed in an immunofluorescence test demonstrated a positive surface reaction with primary CEF and the new cell line but a negative reaction with human or monkey stable cell lines. The pattern of virus suceptibility also confirms that the cells are of chick origin.

Lipid Auxotrophs in Chinese Hamster Ovary Cells

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Specific lipid-requiring mutants isolated from cultured animal cells should serve as unique biological tools for studies of regulation of lipid metabolism. Chinese hamster ovary (CHO) cells seem to be a suitable cell line for this purpose since wild-type CHO cells grow in lipid-free medium. By using the bromodeoxyuridine-light enrichment technique, three different lipid auxotgrophs (designated as clone 49, clone 215, and clone 1) have been isolated from mutagenized CHO cells. Clone 49 seems to contain a structurally altered microsomal stearoyl-CoA desaturase, and is defective in unsaturated fatty acid biosynthesis. Clone 215 is a cholesterol- requiring auxotroph, with enzymatic defect in oxidative demethylation of lanosterol. Clone 1 requires both cholesterol and unsaturated fatty acid for growth. This mutant seems to be defective at the regulatory genetic locus, which controls the derepression of endogenous cholesterol biosynthesis and unsaturated fatty acid biosynthesis. It can be shown that CHO cells possess functional low-density lipoprotein receptors; cholesterol synthesis and unsaturated fatty acid synthesis seem to be coordinately regulated by cholesterol esters contained in low-density lipoprotein. (Supported by N1H Grant HL 21246 and 1P 30 CA 23108-01 A1).

Bile Acids and Mutagenesis

D.A. PAGANO and JON R. GEIGER, Clark Science Center, Smith College, Northampton, MA 01063

Epidemiological evidence suggests that intestinal cancer may be diet related. Additionally, diet has a marked effect upon the intestinal microflora, and on other intestinal components. This study was undertaken to investigate the influence of bacteria on bile acids, by testing the bile acid products of anaerobic metabolism for mutagenicity. The Ames *Salmonella*/microsomal test and the DNA Repair test were used to assay for mutagenicity and DNA damage, respectively. Also, the ability of certain bile acids to enhance the mutagenic response of other compounds was studied by incorporating an azogroup additive dye, methyl orange, in the anaerobic bacterial metabolism system and testing the interaction products.

The results show that bile acids were not mutagenic in both assay systems when tested directly and after anaerobic metabolism. Methyl orange, which has previously given discrepant results between mutagenicity and transformation assay systems, was negative when tested directly. Additionally, tests for bile acid mutagenic enhancement of the dye were also negative. A discussion of alternative modes of action which may involve bile acids in intestinal cancer is included. (Supported by a grant from the Blakeslee Fund).

Hemopoietic Cell Reconstitution of HLC (high leukocyte count) and LLC (low leukocyte count) Mice to Their F_1 Hybrids

CHARLES LERNER, The Jackson Laboratory, Bar Harbor, ME 04609

Two lines of mice, selectively bred to produce a widely divergent white blood cell count, were used to examine one aspect of cellular proliferation. Is the ability of a cell to proliferate dependent upon its host's environment or is it rather an intrinsic property of the cell? An attempt to answer this question was carried out in the following manner.

F_1 hybrids of the High and Low Leukocyte lines were lethally irradiated and reconstituted with either bone marrow or fetal liver cells from the parental lines. Resulting blood counts showed that although these cells were removed from their native environment, they did retain their ability to proliferate true to their parental character. Thus, the cell is seen to control its own destiny.

Terminal Deoxynucleotidyl Transferase Expression in Mice

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Terminal deoxynucleotidyl transferase (TdT) is an enzyme that catalyzes the polymerization of deoxyribonucleotides on the 3'OH end of the polydeoxyribonucleotides. TdT is foremost a nuclear enzyme with a molecular weight of approximately 32,000 daltons, and readily distinguishable from other cellular DNA polymerases. Although the assay is relatively simple in principle quantitative determinations vary by 10- to 50-fold under a wide variety of extraction and assay conditions. Therefore, it is desirable that conditions for extraction and assay be optimized so that enzyme activity in mice can be readily compared. Here we report on the optimized conditions for extraction and assay of TdT using purified murine enzyme.

The Effects of Castration upon Alkaline and Acid Phosphatase Activity in the Mouse Prostate Gland

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Acid phosphatase is present in the acinar epithelium of all lobes of the mouse prostate gland. Brandes and Bourne (1954 and 1963) and Iype and Heidelberger (1968) have reported that while acid phosphatase is present in the epithelial cells, an alkaline phosphatase reaction is seen in the basement membrane and periacinar connective tissue. Our studies on primary culture of the prostate gland from inbred strains of mice includes a search for methods to identify the origins of the cells (i.e., epithelial or connective tissue). The distinction between acinar and periacinar cells in regard to phosphatase staining reactions has been used as a criterion for identifying cells in culture.

When frozen sections of uncultured prostate gland were stained, the earlier results were confirmed. In animals which had been castrated for at least 14 days, the alkaline and acid phosphatase activity was less. There were differences between the dorsal and ventral lobes, and these varied in degree with the length of time since the mice were castrated. Alkaline phosphatase was less in the dorsal lobes, while the acid phosphatase activity was less in the ventral lobes of the castrated mice.

The differences observed in the ventral and dorsal lobes of the castrated and non-castrated animals, as well as the differences in cultured and non-cultured cells, will be discussed.

The Development of Brush Border Transport System in the

Chicken Small Intestine

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Previous studies showed that nutrient (amino acid and sugar) transport in chick intestinal slices peaks 2d after hatch and then declines to adult levels after≃21d. To determine the subcellular site(s) modified during development, we prepared brush border membrane vesicles (BBM) from 2 and 21d chicks and studied transport of ^{3}H-D-glucose and β-alanine into these BBM. With 0.1mM glucose, we found an initial, Na-dependent, rapid uptake of substrate (overshoot) followed by a slower decline to equilibrium levels in both 2 and 21d BBM; maximal overshot values in 2d BBM were twice those found in 21d BBM. With 0.1mM β-alanine, no overshoot was observed, but initial uptakes were greater in 2d BBM than in 21d BBM. Equilibrium levels of 0.1mM glucose, β-alanine and mannitol were the same in 2 and 21d BBM, indicating that they possess the same average intravesicular volume/mg protein. Preliminary kinetic studies with glucose indicated that the V_{max} for specific (phloridizin inhibitable) transport was 2 times higher in 2d BBM than in 21d BBM, but that K_m was the same; 21d BBM also exhibited increased passive permeability to glucose and mannitol. Since intestinal slice studies with 3-0-methyl glucose also showed a higher V_{max} in 2d chicks with little change in K_m, our data suggest that changes in chick intestinal transport with development are a result of a decrease in carrier number or turnover number with some increase in luminal membrane permeability. (Supported by N1H Grant ES-01678, and a grant from the Maine Agricultural Experiment Station).

Coarse Grain Mapping of Base Composition in DNA by Physical Methods

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The mechanism of the thermal denaturation of DNA has been investigated by analysis of high resolution derivative melting profiles obtained by the direct method (BBA, 518, 223-246). Comparatively short, homogeneous DNAs have been examined with special attention given to coliphage λ (cI857s7) DNA. A number of lines of analysis (variation of the solvent conditions, electron microscopic results and the use of restriction enzymes) indicate that the thermal denaturation process consists mainly of multiple, independent two state helix coil equilibria. Segments undergoing these transitions are characteristically 600 to 3000 bp in length. We have produced specific cuts in the λ molecule with various restriction enzymes and fractionated the pieces by base pair specific affinity chromatography. High resolution thermal denaturation of the fragments produced in these digests permits a correlation to be established between physical location of a segment in the molecule and its thermal transition in the deconvoluted melting profile. This information can be used in conjunction with difference profiles and base composition information (from thermal denaturation at 282 nm) to create a coarse physical denaturation map of the λ molecule with respect to local base composition. (Supported by MAES, #315; N1H, GM22827).

Purification of Cytoplasmic Tubulin and Microtubule Organizing Center (MTOC) Proteins Functioning in Microtubule Initiation from the Alga *Polytomella*

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Cytoplasmic tubulin and the microtubule organizing centers (MTOCs) for the cytoskeletal microtubule system of the quadriflagellate *Polytomella* have been isolated. The isolated MTOCs serve as sites for the *in vitro* assembly of the purified tubulin protein, initiating a pattern of microtubules very similar to that of the cytoskeletal system in the intact cell. A brief extraction of the isolated MTOCs with a low ionic strength Tris-EDTA solution results in (apparently) intact but assembly-incompetent MTOCs. The extract contains several MTOC proteins and when mixed with purified tubulin promotes microtubule assembly. The major proteins in the extract (four polypeptides of molecular weights 190,000 to 210,000 on SDS gels) functioning in this assembly have been purified based on their association with tubulin to form sedimentable microtubules. Turbidimetric analysis of assembly combined with experiments following the kinetics of incorporation of *in vivo* ^{35}S-labeled MTOC proteins into sedimentable polymer demonstrate that these proteins function specifically in microtubule initiation and do not contribute to microtubule elongation. These results indicate that microtubule assembly *in vivo* is controlled by microtubule initiating proteins associated with the organelles termed microtubule organizing centers. (Supported by NSERC grant).

DEVELOPMENTAL BIOLOGY

Teratogenicity of Solanine A in the Early Chick Embryo Cultured *in vitro*

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Elsewhere we have described the teratogenic effects of Solanine, and of a preparation of mixed glycoalkaloids from potatoes infected with late blight, *Phytophthora infestans*. We observed various trunk and tail defects including rumplessness, trunklessness, and blisters or hematoma in the trunk or tail region. However, brain abnormalities including anencephaly and spina bifida such as that observed by Renwick and Poswillo in marmosets, were found in only a few cases. Because the failure to obtain these defects may be due to failure of the compound to get into the embryo early enough and in sufficient amounts, we switched from the *in ovo* injection technique to the *in vitro* culture technique. Stage 4 to 7 (H and H) embryos were cultured on agar-albumen media containing various concentrations of solanine A. The embryos were read at 6 to 12 hour intervals for 30 hours. Concentrations of solanine A above .75 mg/ml were toxic to the chick embryo. At a concentration of .03 mg/ml, 11 embryos were alive, and 11 were dead. At a concentration of .015 mg/ml, 9 were alive and one was dead. At these lower concentrations various brain abnormalities (e.g., exencephaly, spina bifida, and defects which could result in anencephaly) were observed in half of the living embryos. Besides these brain abnormalities, blisters or hematomas were also observed in the trunk or tail region in a few (3) cases. These results show clearly that Solanine A can induce various brain abnormalities in the chick embryo. (Cooperative Regional Project NE. 94).

Transplantation of Leg Imaginal Discs and Its Implications on Neuronal Specificity

P. SIVASUBRAMANIAN, Biol. Dept., Univ. New Brunswick, Fredericton, N.B.

How the growing axons find their appropriate target sites on which to synapse is the central question of developmental neurobiology. Insects, with their limited number of neurons and centripetal growth of sensory axons, are most suitable animals for such investigations. Making use of a special ectopic transplantation technique, studies were made on the development of nerve connections between peripheral structures and the central nervous system of the fleshfly, *Sarcophaga bullata*. Transplantation of leg imaginal discs results in the formation of supernumerary legs on the host flies. Microdissection of these legs revealed the existence of nerve connection between the supernumerary legs and the thoracic ganglion of the host fly. When these nerves were backfilled with cobalt chloride it was seen that the nerves projected to the appropriate neuromere in the host ganglion. These studies indicate that the growing nerves from the imaginal discs can locate and project to the proper areas of the host's central nervous system.

Some Characteristics of the Fertilization—Incompatibility Factor in Mormoniella

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Non-reiprocal cross incompatibility in the parasitic wasp *Mormoniella (Nasonia) vitripennis* is characterized by the failure of sperm from wild-type stocks to successfully fertilize eggs from cer-

tain stocks marked by eye color mutations. The failure of fertilization is characterized by formation of a tangled mass of chromatin, instead of normal chromosomes, from the sperm pronucleus. The eggs then develop normally into haploid males. The incompatibility is maternally transmitted, and is inherited independently of the eye color mutation with which it was originally associated. It can be introduced into wild-type females by injection of homogenetes prepared from incompatible stocks, and the causative factor can be cultivated in chick embryo sacs. Following development of a means of raising Mormoniella larvae in culture media, it was shown that addition of tetracycline to the media in a concentration of 0.025 mg/ml rendered wild-type males able to produce sperm which could successfully fertilize eggs from stocks with which they are normally incompatible. It is suggested that a rickettsia-like organism is responsible for the incompatibility, as has been proposed for similar phenomena in *Culex pipiens*. (Supported by NIH).

Homozygous *Ay* Expression in Strain 129/Sv-*Ay* Mouse Embryos

N.H. GRANHOLM and L.C. STEVENS, The Jackson Laboratory, Bar Harbor, ME 04609

The onset of expression of *Ay* homozygosity appears to depend in part upon the genetic background. Accordingly, clues to basic biochemical alterations specified by *Ay* may be forthcoming through an analysis of *Ay*/*Ay* embryos in different strains. The objective of this study was to characterize the developmental potential of strain 129/Sv-*Ay* embryos *in vitro* and *in vivo*. Results from histological examinations show that *Ay* homozygotes are totally resorbed or severely degenerate at 5.5 days of gestation. Quantitative analyses of cell numbers per embryo at 108 hours of gestation indicate that inner cell mass (ICM) cells are preferentially affected by *Ay*. Counts of ICM nuclei per embryo in experimental matings (43.0 ± 2.7, $n = 30$ embryos) were significantly lower ($p < 0.05$) than those from control matings (59.6 ± 2.8, $n = 34$ embryos). Data from embryo culture show that *Ay*/*Ay* embryos develop to expanded blastocyst stages but then fail to hatch and outgrow. Significant differences ($p < 0.01$) were found between control and experimental groups with respect to hatching and outgrowth. Apparently *Ay* homozygosity is similarly expressed on both C57BL/6J-*Ay* and 129/Sv-*Ay* backgrounds. However, subtle differences between the two strains may be revealed by careful analyses of *Ay*/*Ay* embryos over the early implantation period. (Supported by National Cancer Institute Grant CA-02662 LCS and Eagles' Ehrmann Cancer Fund NHG).

Effects of Age and Transplantation on Hemopoietic Stem Cell Lines

D.E. HARRISON, The Jackson Laboratory, Bar Harbor, ME 04609

Whether marrow cell lines have limited lifespans is a fundamental question in immunohematological development and aging. After transplantation into young recipients, marrow cell lines from old and young donors produce erythrocytes equally well. With successive serial transplantation, functional abilities declined, even in unirradiated recipients, but the same pattern is followed by cell lines from old and young donors. The longest lived cell lines have functioned normally and cured serial W-anemic recipients for over 3000 days in 4 or 5 transplantations. When stem cell mixtures of two distinguishable types are transplanted into the same recipient, their relative repopulating ability is rigorously tested. Stem cell lines from old and young donors had similar repopulating abilities, but after a single transplantation, repopulating abilities declined substantially. A single transplantation causes much more decline than does a lifespan of normal functioning, even using transplantation procedures designed to cause minimal damage.

Developmental Genetics of Anophthalmia in Mice

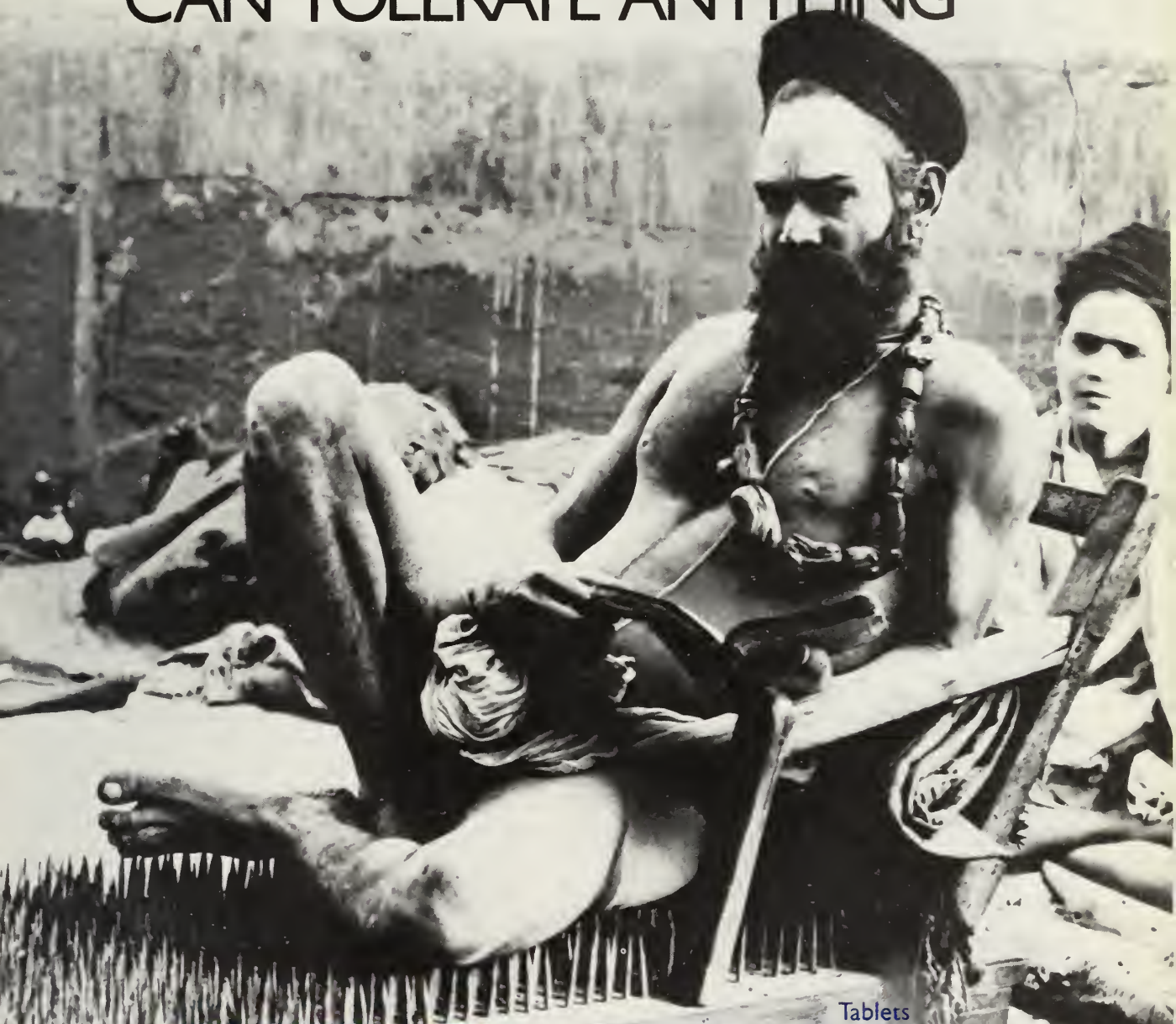
H.B. CHASE, C. HORCH, J. NOVY, and N.I. GONSALVES, R.I. College, Providence, RI 02908; Brown Univ., Providence, RI 02912

In re-investigating development in the eye region of mice of the inbred anophthalmic strain (ZRDCT/Ch), it has been discovered

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BETTMANN ARCHIVE

that development is normal to Day 10 (26 somites) and even that a lens is induced (Horch *et al.*, Dev. Biol. 63, 1978). The lens, however, is small and is generally not well-centered with respect to the optic cup, resulting in no further eye formation or in varying degrees of microphthalmia (20-30%). A significant observation is that the cup has a closed C shape in the anophthalmic strain and in some control strains but an open C shape in other strains at equivalent stages of development, suggesting that a normal lens-cup interaction may be more easy of attainment in the open C situation and thus explain differences in "threshold" when the eyeless strain is crossed with various normal control strains. Using successive backcross generations from an original open cup line (C_3H) with the anophthalmic line and using only fully eyed segregants back to the eyeless strain, there is indeed evidence by generation 5 to 8 that the progeny are either fully normal or bilaterally eyeless with very few intermediate microphthalmics compared to the progeny of earlier backcross generations. Electrophoretic studies as well as EM investigations of embryonic lens and cup areas in the basic strain are being continued at Brown University and at Rhode Island College.

Hormonal Control of Maturation in Starfish Oocytes

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Starfish oocytes will undergo nuclear, cytoplasmic and surface maturation when treated with the ovarian hormone 1- methyladenine (1-MA). Nuclear maturation, or germinal vesicle breakdown (GVB), induced by 1-MA is inhibited by caffeine, theophylline or theobromine. Inhibition was reversed when the oocytes were washed and reincubated with 1-MA. The rate and amount of ^{3}H-1-MA taken up by the oocytes was depressed in the presence of these inhibitors. In a double label experiment the rate and amount of ^{14}C-caffeine and ^{3}H-1-MA taken up was depressed in the presence of each other; however, the rate of uptake was parallel. Unlabeled theophylline, theobromine, 1- ethyladenine and caffeine inhibited the uptake of ^{14}C-caffeine. These, and other data, demonstrate that caffeine, theophylline and theobromine compete for the hormone receptor on the oocyte surface. The effects of these compounds to interfere with cytoplasmic and surface maturation was also examined. Cytoplasmic maturation was studied by examining the ability of sperm to elicit the fertilization membrane reaction. Fewer than 7% of the oocytes incubated in these three compounds in the presence of 1-MA failed to raise a fertilization membrane upon insemination, whereas 77% of the oocytes matured with 1-MA had fertilization membranes. The effects of these compounds on surface maturation was examined by testing the ability of sperm to attach to oocytes. Oocytes treated with 1-MA, caffeine, theophylline, theobromine, or caffeine plus 1-MA, had fewer sperm attached than did oocytes receiving no treatment. It is concluded that caffeine, theophylline and theobromine are hormone analogs capable of inducing surface maturation, but not nuclear.

HUMAN GENETICS

Biotin-Responsive Lactic Acidosis

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A two-year-old white male was in good health until age 15 months when he developed acidosis and dehydration following a mild gastritis. He responded well to fluid therapy. At age 22 months, he presented in severe acidosis following a flu-like illness. His admitting laboratory studies included plasma pH of 6.9, lactate of 52 ng/dl (N = 0.3-12), pyruvate of 3.3 ng/ml (N = 0.3-0.7), and elevated blood alanine. After stabilization he was managed with an oral buffer solution and 300 mg of thiamine/d. He continued to have acidosis, ataxia, and tachypnea. On initiation of 10 mg biotin/d his symptoms resolved. A male sibling died with severe acidosis at age 13 months following a brief respiratory illness. Results of enzymatic studies in pyruvate/lactate metabolism will be presented.

Further Studies on Gonadal Dysgenesis. An Hypothesis on the Pathogenesis of the Somatic Abnormalities

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Laparoscopy on two patients with Turner stigmata, 45 X karyotypes, and good sexual development showed fibrous gonads with few follicles (including a corpus luteum). Cell cultures of one patient's paraovarian fibroblasts showed 45 X chromosome patterns in all mitoses. Buccal smear on a patient with 46 XXq- (46 X del X (q12) showed no sex chromatin, in keeping with the hypothesis that inactivation requires the centromeric portion of Xq. Karyotype of skin fibroblasts on this patient is pending. This girl has streak gonads but few of the somatic Turner stigmata and is 157.5 cm. tall. Turner phenotypes in reported patients with 46 XXq- may result from cell lines with 45 X. We propose that the somatic stigmata of Turner's syndrome result from random inactivation of the only X of cells during development, with resulting death of that cell line. The randomness of the process will explain the wide phenotypic variability in classic Turner's syndrome, and the lethality of the mechanism to early embryos explains the high fetal wastage. This hypothesis requires that in normal cells there is interaction between loci on both X's (on Xq?) to prevent inactivation of the last X. The report (Ped. Res. *12*:457, 1978) of a 46 XYp- phenotypic female with Turner stigmata suggests that loci on Yp may serve this function in the male. If this mechanism is responsible for Turner stigmata in patients with 46 X,i(Xq), then somatic cell lines with no Xp must be nonviable.

Psycho-social Issues in Genetic Counseling of Hemophilia Carriers

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Genetic counseling was given to 60 women after carrier testing in the New England Area Comprehensive Hemophilia Center in a two year period. An analysis of this experience provided us with a mechanism for delineating some of the factors that have to be considered by probable carriers who are wrestling with the tremendous emotional burdens which they feel.

The carrier has three options—taking a chance, remaining childless, or planning gender of offspring. Under each option, however, the psycho-social, economic, physical, medical, and philosophical issues that were introduced for discussion were manifold. Major concerns encompassed amniocentesis, abortion, grief and guilt, sterilization, adoption, jeopardy of the male-female alliance, societal and family pressures, birth control, and the agonizing need to make a decision. Other personality and conditioning factors interconnected with these major issues.

The treatment aspect of genetic counseling was aimed at facilitating the decision-making process for the consultant by separating multifaceted problems and addressing them individually, and by defining priorities so that choices became clearer. The importance of the social worker "picking up the pieces" is evident by the requests we often now receive for repeat carrier testing because probable carriers did not previously receive help in dealing with the information that had already been given them.

Clinical and Cytogenetic Manifestations of Balanced X-Autosome Translocations

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According to the Lyon hypothesis, in human somatic cells, X chromosomes in excess of one are inactivated early in intrauterine life. In cytogenetic studies utilizing autoradiography and BrdU terminal pulse, late replication implies inactivation. In balanced X-autosome translocations, the general rule is that the normal X chromosome is late replicating. Exceptions to the rule have been reported, with inactivation occurring in the Xt in a portion of the cells examined. We have reported the first balanced X-autosome translocation in which there is no late replicating X in ⅓ of cells analyzed.

A Female With 45, X/46X + Frag: A Case Study

ROBERT B. TANGUAY and ROBERT W. SCARLATA, Pineland Center, Pownal, ME 04069

This patient was born in 1966. Delivery induced at 34 weeks because of moderate toxemia. Birth weight was 3 lbs., 9 ounces. Infant became icteric and on day 7 the serum bilirubin rose to 30mg/dl. Jaundice disappeared after 2 exchange transfusions. The admission physical exam. revealed a female with somewhat ambiguous genitalia. After 3 months duration, the patient was discharged. Diagnosis included (1) hyperbilirubinemia, etiology unknown, (2) Cerebral Agenesis (diagnosed by pneumoencephalogram), (3) Intersex problem, (probably pseudohemaphrodite). At age 6 years the patient was admitted to a State mental retardation facility with severe mental retardation associated with hyperbilirubinemia. A buccal smear revealed only 3% cells with chromatin body. A non-banded blood chromosome culture (1972) showed two evenly distributed cell lines; 45,X /46, X + frag. and subsequently was diagnosed as Turner's syndrome. During a genetics evaluation, clinical findings were inconsistent with that of Turner's syndrome and repeat chromosome studies were requested. Chromosome culture (1978) using both GTG and Q banding identifies the fragment and possibly explains the 45, X cell line. The fragment fluoresces when treated with quinicrine didhydrochloride which suggests a partial deleted Y chromosome. This fragment is randomly located within the spread or appears attached to a D group chromosome. A possible mosaic chromosome impression of 46, XYp-/45, X t (YqDq) is presented suggestive of Gonadal Dysgenesis.

Detection of Carriers of Christmas Disease (Hemophilia B) by Immunologic Assay of Factor IX

HENRY C. YANG, POMEROY SINNOCK, and LINDA LaROCHELLE, New England Area Hemophilia Center, The Memorial Hospital and Dept. of Medicine, University of Massachusetts Med. Center, Worcester, MA, and Genetic Counseling Center, Ellsworth, ME 04605

Discriminant values were derived from the factor IX procoagulant and antigen measurements in 30 normal females and 28 obligate carriers of Christmas disease, 21 of whom were from low antigen pedigrees and 7 of whom were from excess antigen pedigrees. Using the criteria of 90% probability of carriership, 19 out of 28 (68%) carriers were correctly identified whereas only 16 out of 28 (57%) were correctly identified if only the procoagulant values were used. In the excess antigen pedigree subgroup, the correct identification rate improved from 3 out of 7 (42%) to 7 out of 7 (100%) by use of the antigen data in addition to the procoagulant values. Factor IX antigen measurements in addition to procoagulant measurements appear to be most useful in the detection of carriers in excess antigen pedigrees.

Retinitis Pigmentosa in Maine: An Outreach Program

C.H. BUNKER, Genetic Counseling Center, Bar Harbor, ME 04609

The term Retinitis Pigmentosa describes a number of hereditary disorders characterized by night blindness and progressive tunnel vision. These disorders differ in mode of inheritance, age of onset, rate of progression and associated complications. Because of this genetic heterogeneity, few of the estimated 500 affected Maine families have received appropriate genetic counseling. Through this program we are able to provide the extensive family history analysis, detailed clinical evaluation, laboratory and electrophysical testing and interpretive expertise necessary to identify specific genetic types of retinitis pigmentosa, and to diagnose preclinical cases. An outreach approach has been utilized to overcome the lack of awareness of availability of retinitis pigmentosa related genetic services, and to facilitate delivery of services to this handicapped population. Since the nearest provider of these services is in Boston, this project may serve as a model for provision of scarce, unique genetic services on a regional basis. The reaction of participating families to this project has been strongly positive.

Pedigree Analysis of French Canadian Populations

M.M. FOLLETT and T.H. RODERICK, The Genetic Counseling Center, Bar Harbor, ME 04609

Genetic heterogeneity presents major difficulties for precise medical diagnosis and genetic counseling. Closed populations offer a means to determine if a genetic problem in a population has more than one genetic origin. Retinitis pigmentosa (RP) has different genetic causes, and may have a relatively high frequency in French Canadian populations. The French Canadian population even though large is a reasonably closed population. Vital records are well preserved for these groups and therefore permit extensive pedigree compiliation and analysis. We have extensive pedigrees on 18 families of French Canadian descent with recessive RP. These identifications and knowledge of the locations of migrating descendants helps to identify geographic areas of higher risks for RP. The tying together of pedigrees helps to understand the extent of variable expression of a single genetic problem.

Laurence-Moon and Biedl-Bardet: Family Studies

R.P. HAYES, and M.M. FOLLETT, The Genetic Counseling Center, Bar Harbor, ME 04609

Syndromes involving mental retardation, pigmentary retinopathy, polydactyly, obesity, hypogenitalism and spastic paraplegia have been identified and evidence has been presented differentiating Laurence-Moon Syndrome from Biedl-Bardet Syndrome. In the present paper, 10 individuals involved in a larger project providing services to families with retinitis pigmentosa are considered and their presenting diagnoses reviewed. All are affected with retinitis pigmentosa in combination with some of the symptoms listed above. Variability of symptoms in three male sibs and in two individuals determined to be related through an extensive pedigree search is demonstrated and the difficulties this raises in diagnosis are discussed.

New Evidence in Usher's Syndrome?

W.C. BROMLEY, Ellsworth, ME 04605

The syndrome of congenital deafness with the progressive vision loss of retinitis pigmentosa is a well recognized, recessively inherited disease (Usher's Syndrome). Related diseases are reviewed. A pedigree presentation and case study is discussed, demonstrating possible heterogeneity in this disease. Implications in regard to investigations and genetic counseling are made.

Y Chromosome Aberrations in Childhood Leukemias

T. PADRE-MENDOZA, P. FARNES, B.E. BARKER, P. SMITH, and E. FORMAN, Departments of Pathology, Pediatrics, and Oncology, Rhode Island Hospital and Brown University, Providence, RI 02902

Y chromosome loss was documented by chromosome banding techniques in bone marrow blast cells of two leukemic male children. One patient had acute myeloid leukemia of t(8;21) type. The other patient had leukemia established as lymphoid by multiple characterization parameters. The importance of chromosome banding techniques in characterization of childhood leukemias is further illustrated by a third patient with Ph' positive acute myeloid leukemia, in whom an additional Yq- (short Y) resembled a second Ph' chromosome by unbanded karyotype. The studies provide evidence that Y loss occurs in childhood leukemias, and that Y loss occurs in non-myeloid leukemias.

Chronic Ranulocytic Leukemia and Carcinoma of the Cervix In Situ Following Renal Transplantation

R.L. HILARIO, T. PADRE-MENDOZA, and M.M. ALBALA, Div. Clinical Hematology, Dept. Medicine, and Section Gytogenetics, Dept. Pathology, Rhode Island Hospital, and Brown University, Providence, RI 02902

A 26-year-old white female presented with Philadelphia (Ph') chromosome positive chronic granulocytic leukemia 5 years after successful renal transplantation and prolonged therapy with Azathioprine and Prednisone. This patient represents the 7th case of CGL reported within the population of immunosuppressed renal transplant recipients. Of further interest in our case is the development of carcinoma in situ of the cervix 2 years following the transplant. Although multiple malignancies have been recognized in renal homografts, the occurrence of CGL and Ca in

situ in the same patient has not been previously described. A possible mechanism for the development of CGL is the association of chromosome damage by Azathioprine and immunoparalysis of the host, thus setting the stage for the emergence of a malignant clone. The importance for close follow-up of patients on prolonged immunosuppressive therapy is emphasized.

Personality and Familial Correlates of Adaptation to Genetic Counseling

J.. LIBERATORE, L.G. GOODMAY, W.G. McINTIRE, and L.J. BEAUREGARD, Dept. Human Development, University of Maine and Eastern Maine Medical Center, Bangor, ME 04401

The reported study was diagnosed to examine the relationship between locus of control, individual self-concept, selected family structure variables, and perception of the genetic counseling experience of the population of adult patients seen at the Eastern Maine Medical Center Genetics Counseling Clinic during the 1978 calendar year. Fifty-nine of 133 mailed questionnaires were returned by 45 female and 14 male patients. Forty-nine (37 female, 12 male) were usable. It is hypothesized that (1) high self-concept, internal locus of control, and supportive family structure each is predictive of understanding of, integration of, and adaptation to the information provided during the counseling process; (2) that these traits also are predictive of positive evaluations of the specific counselor seen by the patient and the counseling process; and (3) that these traits predict appropriate behavioral response to the genetic information transmitted in terms of subsequent contraceptive-family planning behavior.

Experiences with Prenatal Diagnosis of Genetic Disorders at Eastern Maine Medical Center

L.J. BEAUREGARD and A.N. LAMB, Genetics Laboratory, Eastern Maine Medical Center, Bangor, ME 04401

During our first four years of operation, more than 275 mid-trimester amniotic fluid specimens have been tested as a means of prenatally diagnosing genetic disorders. Utilization of this service has increased rapidly during this period and has paralleled nationwide trends. Indications for testing have also reflected national trends with nearly 70% assigned to maternal age of 35 or more associated with increased risk of bearing a child with Down syndrome. Diagnostic information was obtained in more than 95% of cases with an average culture time of 18 days. No diagnostic errors have been recognized during follow-up. Among completed studies, 94.4% suggested a chromosomally or biochemically normal fetus. Balanced translocations or inversions, similar to that found in one normal parent, were observed in 1.2% of cases. Only 2% of cases contained an abnormal karyotype which was expected to result in a clinically recognizable abnormality. In the remaining 2.4% of studies, mosaic karyotypes were observed. In most cases, the mosaic cell line could be explained as a culture artifact; in others, they presented a definite diagnostic dilemma since pregnancy outcome could not be adequately predicted.

Cleft Lip and Cleft Palate: Recent Advances in Mouse Models and Implications for Human Research

D.M. JURILOFF, The Jackson Laboratory, Bar Harbor, ME 04609

Cleft lip ± cleft palate (CL(P)) and isolated cleft palate (CP) are threshold traits that occur in mice and human beings. The etiology of CL(P) in both species shares many features: simply inherited, possibly homologous syndromes; a large non-syndromic class with multifactorial origin and with face shape as the possible underlying variable; higher frequencies of CL(P) in abortuses than in newborns; a relatively small role of environmental factors, with the exception of diphenylhydantoin; evidence for a gene within the multifactorial system that makes a major contribution to risk. Given the similarity between species, identification of the action of the major gene in mice may provide a means of preventing CL(P) in human beings. Isolated cleft palate in the two species is also similar: there are several threshold variable and many known syndromes; the multifactorial class involves more environmental effects than for CL(P) and is probably genetically complex; the major histocompatibility locus is involved.

Partial Deletion of the Short Arm of Chromosome #9 (9p- Syndrome): Case Study

R.W. SCARLATA, and R.B. TANGUAY, Pineland Center, Pownal, ME 04069

Presented is a case study of a 19-year-old female who since birth has been suspected as having Down's Syndrome. She is short statured, has a reduced head circumference with flattened occiput, mongoloid palpebral slant, epicanthal folds, Brushfield spots, short neck, hyperextensibility of the joints, wide space between the first and second toes, and is mentally retarded. There are, however, two noteworthy exceptional findings, i.e. trigonocephaly and arachnodactyly. A non-banded chromosome analysis in 1970 revealed 46,XX.

In 1978, during routine in-patient genetic screening, it was decided to repeat these studies including a fibroblast culture. The lymphocyte and fibroblast cultures (GTG banding) both revealed 46,XX del(9) (p22). Also, presented is a review of eleven cases of 9p- Syndrome. Elliot et al (1970) reported a case of a C-group chromosome abnormality (? 10p-). In retrospect, there were features in this case suggestive of the 9p- Syndrome. Kistenmacher et al in 1970 described a case of ring C-chromosome with similar clinical features to 9p-. As of 1976, Alfi had described a total of six cases of 9p- Syndrome of which two were suspected prior to cytogenetic confirmation. Alfi and colleagues commented that this syndrome is probably not as rare as suggested by the infrequent number of cases reported. The deleted segment is small and has been missed using the non-banded techniques. It is also our feeling that there will be increased reporting of cases of 9p- Syndrome in the future as cytogenetic techniques are refined and this syndrome becomes more well known.

INTRODUCTORY COLLEGE SCIENCE TEACHING

Environmental Science for the Nonscience Major in the Context of a Business College

DIANE MAY, Husson College, Bangor, ME 04401

An environmental science course taught in a business college can effectively integrate business theory and economic principles with the principles of ecology. The role of the instructor is to present the student an objective explanation of the principles of ecology. It is necessary that this portion of the course be definitive rather than emotional and that the popular misconceptions of ecology be separated from fact. Outdoor activities which include use of local resources are used to illustrate the principles (e.g., sea coast, lakes and streams, rock quarries, sanitation plants). With a comprehensive background in ecology the student is then presented issues that are relevant to his/her interest and experience. The student role becomes one of analysis and decision-making. He/she can apply his/her knowledge of business theory, economics, and ecology and make a rational decision on an issue. The instructor serves as a mentor by guiding the thought processes of the individuals. The student also has the experience of presenting oral and written reports on an issue to the class. This allows for further investigation of an issue by the student and provides him/her the challenge of persuading a group to arrive at the same decision. Finally, it is possible for the instructor to compare the course objectives with the course outcomes and statistically assess the value of the course within the framework of the college.

A Two-year Core Program in Biology

MIRIAM F. BENNETT, Dept. of Biology, Colby College, Waterville, ME 04901

During the first two years of his or her undergraduate career, a Biology Major at Colby College usually completes a required set of courses in preparation for advanced work at the Junior and Senior levels. The courses of the Two-year Core are Introductory Chemistry, the Calculus and four, semester courses in Biology. The first course in Biology focuses upon the structure, function and behavior of organisms. The second course emphasizes reproduction, heredity and development of plants and animals. During the third semester in Biology, a major studies Ecology and Evolution, while the structure and functions of cells are the subjects of the fourth semester of the Biology Core. The laboratory work associated with each of the courses stresses the use of methods and

instruments important to the field; the importance of observation and experimentation; and, the analyses and communication of results of the students' work.

Teaching Science—The Process and Its Products—in the Laboratory

JON C. GLASE, Neurobiology and Behavior, Cornell University, Ithaca, NY 14853

Science courses have an important responsibility to teach students not only about the *products* of science, but also the *process*. This knowledge is essential to a better understanding of the nature of science and of what science can and cannot do for society. The major emphasis of the laboratory portion of any science course should be to actively involve the student with scientific thinking and methods. As an approach to this end an introductory biology course at Cornell University is given as an example of the opportunities and problems in teaching science in a laboratory setting. In addition, the objectives and activities of a new organization of laboratory biology teachers will be presented as an example of the virtues of cooperation among college science teachers.

Problems of Teaching Drug Courses at the College Level

C.W. MAJOR, Zoology Department, University of Maine, Orono, ME 04469

Drug courses at universities lacking medical schools and maintaining limited graduate schools constitute a special subset. Courses aimed at the graduate level have a basic problem in attracting an audience, since there is a general lack of feel for the pharmacological approaches. On the other hand, the more general "Drug Abuse" course aggravates upper division students whose biochemical and physiological knowledge is substantial. Our course started as a graduate "Introduction to Pharmacology," found only a weak market, and, subsequently, was converted to a general audience drug abuse course but with a prerequisite of a semester of basic biology. Enrollments promptly rose to 125 and steadied at 75-95 each year. The simple one semester prerequisite requirement apparently acted as a red flag and the student enrollment turned out to be biology and zoology majors. After the first year there was an influx of nursing and nutrition students. The audience being more sophisticated than predicted, the level has crept upward and objectives have been modified. The course now consists of basic pharmacological distribution principles, a survey of OTC analgesic and cold therapies, moving then into narcotic analygesics, sedative hypnotics, anesthesias, and analeptics, stimulants, psychotherapeutic drugs, and the hallucinogenic compounds. The approach then changes to disease-oriented units with ulcer treatment, epilepsy, the pill, cardiovascular drugs, antibiotics, carthartic etc. Some of the problems associated with credibility and teaching level will be discussed. There is some evidence of a "sophisticated" consumer attitude amongst the students currently enrolled.

A Synthesis of Traditional and Audio-Tutorial Teaching in Basic Biology

JAMES WADDELL, Dept. Zoology, University of Maine, Orono, ME 04469

The problems of teaching basic biology to a large body of students with very varied backgrounds and needs are outlined. Described are the ways used to cope with these problems at the University of Maine at Orono. The mechanisms dealt with include: modularizing the subject matter; alternate and supplementary modes of instruction; convenience scheduling of audio-tutorial laboratory instruction; self-scheduling of exams by students; multiple examination opportunities by using computer generated exams and variable pacing and variable credit possibilities. Some useful experiences are also recounted.

The Use of the Investigative Laboratory in Introductory Biology

LOUIS V. WILCOX, JR., Unity College, Unity, ME 04988

The Investigative Laboratory is intended to engage the student in the process of active investigation whereby the student will develop an understanding of how science is generated. Furthermore, this approach frees the student from normal course obligations to develop his own conclusions and integrate them into a wider area of knowledge. Utilization of this approach at three different undergraduate institutions demonstrated that 1) substantial bibliographic instruction is essential; 2) the subject of investigation should be in the instructor's area of competence; 3) the investigation should cover a substantial period of time— optimally a full semester; and 4) the student must select and define his own problem for investigation.

This method of laboratory instruction motivated students more than traditional methods used in introductory biology; resulted in the development of more effective work habits; and gave students a better grasp of both the knowledge and the process of the science of biology than a lecture/laboratory approach.

NUTRITION

Common Nutritional Problems Associated with Cancer

DERRY ANN MORITZ and NANCY S. SUSKI, Regional Visiting Nurses Agency, 855 Howard Ave., New Haven, CT 06520

Nutritional assessment will be described in reference to various physiological, physical, and psychosocial parameters. The results of a nutrition study which investigated the eating patterns of 99 individuals with cancer clarify the most commonly occurring nutritional problems; and these subjects' recommendations combined with the speakers' professional experiences provide practical approaches to the management of nutritional problems.

In addition, selected misconceptions around nutrition and the persons with cancer will be discussed; implications will be drawn regarding suggested communication pathways among health professionals.

A Common Mechanism for the Tumor Inhibitory Actions of Vitamin A and Arginine

E. SEIFTER, G. RETTURA, and S.M. LEVENSON, Dept. Surgery, Albert Einstein College of Medicine, Bronx, NY 10461

We have reported that supplemental arginine (1%) and supplemental vitamin A (150 units/g food) each have prophylactic and therapeutic effects in mice inoculated with C3HBA adenocarcinoma cells or with Moloney Sarcoma Virus (MuSV-M). We examined the influence of vitamin A and arginine on some aspects of the hosts' immune system since these tumors are immunogenic and resistance to them is decreased in immuno-incompetent animals. MuSV-M inoculation and tumor growth lead to progressive thymic involution resulting in a decrease in small lymphocytes of the thymus from $20x10^6$ cells to $9.0x10^6$ cells in 14 days. Such a decrease does not occur in MuSV-M inoculated mice fed either supplemental arginine or vitamin A ($p < 0.001$ in each case). We found also a progressive and statistically significant reduction in the lymphocyte: neutrophil ratio in peripheral blood of mice inoculated with MuSV-M (73:27 at day 0, 55:45 at day 3, 44:56 at day 10 and 40:60 at day 14, beginning at the time of MuSV-M inoculation, this ratio remained close to normal and never fell below 60:40. Similar results for the thymic small lymphocytes and peripheral WBC's were found in mice inoculated with C3HBA cells and treated with arginine or vitaminaA. We believe that arginine and vitamin A (1) prevent lymphocytic destruction due to tumors, and (2) favor lymphocytic and macrophagic activity against the tumors. (Supported in part by NIH grants GM 17423, 5K06 GM14208, and Dept. of Army Cont. DADA 17-70-C).

Randomized Control Trial of Hospital Nutritional Support During Abdominal Radiotherapy

A. BOTHE, JR., D. VALERIO, B.R. BISTRIAN, and G.L. BLACKBURN, Nutrition Support Service, N.E. Deaconess Hosp., Boston, MA 02215

In a prospective clinical study, 32 patients receiving abdominal radiotherapy were randomized to receive total parenteral nutrition (1-2 gm protein/kg, 40-45 kcal/kg/day) via

a central venous catheter or to receive ad lib oral feeding. Nutritional assessment was performed before, during and at the completion of therapy. Data were also collected on tumor type and stage, amount of pre-treatment weight loss, dose and goal of radiotherapy, and the response to treatment. Despite more abnormal initial assessment parameters, TPN was able to maintain nutritional status during radiotherapy and to maintain or restore immunocompetence. However, mortality was noted to be more frequent in patients receiving only palliative radiotherapy regardless of nutritional or immune status or nutrient input. Further studies are required to define the precise role of TPN during oncologic therapy. A cautious approach to this complex relationship is necessary so that nutritional therapy is instituted only in situations of benefit to the patient usually associated with effective antineoplastic therapy.

Role of Anorexia in Development of Cancer Cachexia

J. WADE, A. BOTHE, JR., B.R. BISTRIAN, and G.L. BLACKBURN, Nutrition Support Service, N.E. Deaconess Hospital, Boston, MA 02215

A retrospective analysis of 26 cancer out-patients receiving radiation with/without chemotherapy was made to assess the prevalence of inadequate dietary intake and changes in nutritional status. Dietary interviews and 24 h dietary recalls commonly revealed food aversions and protein-energy intakes below individual requirements. Body composition measurements showed an average pre-treatment weight loss of 21%, and subnormal values for triceps skinfold thickness and arm muscle circumference reflecting protein-calorie malnutrition.

Following initial assessment, all patients received diet as tolerated and nutritional formula supplementation throughout radiation therapy. Daily food diaries indicated that spontaneous food intake provided from 25-51% of caloric needs. Formula supplements provided remaining calories. Serial measurements showed that weight loss was arrested but there was no significant change (i.e., reversal) in any objective assessment parameter.

Conclusion: Anorexia is a common feature in the weight loss associated with cancer. Formula supplementation can prevent further deterioration in nutritional status during out-patient radiotherapy, thus suggesting that nutrient intake is a significant variable in cancer cachexia. Invasive feeding techniques (feeding tube, TPN) would probably be necessary for nutritional repletion.

Defining Inbred Syrian Hamsters for Cancer Research

F. HOMBURGER, C.G. VAN DONGEN, H. SOTO, and R.A. ADAMS, Bio-Research Institute, Cambridge, MA 02141

Exceptionally low spontaneous tumor incidence of hamsters renders species ideal for carcinogen bioassay, provided inbred strains or hybrids are used which are susceptible to class of carcinogens studied. Syrian hamsters of various inbred BIO lines show strain-specific susceptibility or resistance to polycyclic hydrocarbons, β -naphthylamine, both not inducible in rats and mice. Strain-specific target-organ factors determine susceptibility and outcome of tests.

Other modifiers of carcinogenesis in hamsters are similar to those known for other rodents, including sex (influencing mammary cancer induction and that of intestinal tumors).

Naturally occurring carcinogens and chemical contaminants of commercial diets may be uncontrolled modifiers of carcinogen bioassay, which calls for development of semi-synthetic diets appropriate for hamsters.

Impact of these variables on interpretation of test results obtained with hamsters in carcinogen testing and problems of extrapolation to man will be discussed.

Animal Models and Studies as Predictors of Carcinogenic Risk

H.F. KRAYBILL, National Cancer Institute, Bethesda, MD 20205

The significance of pronouncements in scientific reports and even lay publications concerning the carcinogenic properties of an environmental chemical (food additivies, drugs, cosmetics, industrial and agricultural chemicals) is dependent or should be dependent upon the quality of the tests performed implicating that agent from a potential hazard viewpoint. In general, a biological response, including carcinogenesis, observed in animals cannot be unequivocally extrapolated in terms of actual risk to man. Various limiting factors such as improper test species and strains, test chemical contaminants, metabolic overload or overdosing, improper route of administration, influence of hormones and diet, and the potential for repair mechanisms condition the response and, thus, in turn the interpretation of bioassay findings. Understatement and overstatement of risk is one of the end products of faulty experimental design and misinterpretation of data and findings. A coalition of all factors with an ultimate appraisal of all variants should provide for a better perspective on risk and a more balanced evaluation of the true carcinogenic activity and potency, if any. The discussion attempts to clarify how misinformation and misinterpretations are developed.

Knoxville—PSYCHIATRIST—EXCELLENT PROFESSIONAL OPPORTUNITY, large Neuropsychiatric hospital, immediate vacancies for Board Certified/Eligible Psychiatrist. Strong support staff and facilities. Enjoy benefits of 30 days paid vacation, 15 days paid sick leave (accumulating) per annum; liberal retirement plan; health and life insurance; malpractice shelter; moving expenses paid; HIGHLY COMPETITIVE SALARY to $50,000 with qualifications, license in any state. Contact: Chief of Psychiatry, VA Medical Center, Knoxville, Iowa 50138 Phone: (515) 842-3101, extension 216. EOE

Medical Practice Expenditure Study Under Way - - -

A scientifically selected random sample of approximately 12,750 physicians in eighteen different specialties will be contacted soon for a brief telephone interview by staff members of the National Opinion Research Center. These interviews will mark the beginning of the third year of a five-year research study of medical practice expenditures. The study, endorsed by the American Academy of Pediatrics, is aimed at bringing about better health insurance reimbursements in the face of inflationary practice costs.

One Hundred Twenty Sixth Annual Meeting At Rockport - - -

Two hundred Maine physicians and their families gathered at the Samoset Resort in Rockport for the 126th Annual Session of the Maine Medical Association, June 16-19. Long business sessions and a fine scientific program were sandwiched between social and recreational activities. Reports of the House of Delegates' meetings and reference committees, including resolutions and news of a $40 assessment to cover legal fees and operating costs for the current year and a $100 dues increase for 1980, will appear in a Fall issue of The Journal.

Dr. Valentine J. Moore of Waterville was gold medal winner in the 3 mile Maine Medical Mixed Masters road race, and Dr. Robert McAfee's Cumberland County Medical Society team outswam Dr. Gilbert Grimes' Androscoggin County group for back-to-back water polo victories.

The Medical Mutual Women's Tennis Tournament was won by Mrs. William Maxwell and Mrs. Patrick Dowling who bested Mrs. John Towne and Mrs. Raymond Culver in the final round.

The Men's Doubles Tournament was won by Dr. Carl Brinkman of Portland and Dr. Frank Twadelle of Gardiner over Dr. Cheong Leong and Dr. Miguelito Cabelin of Lewiston in a postponed match completed in Brunswick on June 30.

The Medical Mutual Golf Tourney was won by Dr. Charles R. Geer of Portland; MMA President Brinton T. Darlington, M.D., of Augusta was the second place finisher; there was a third place tie between Dr. Patrick Dowling of Portland and Mr. Rocco Maffei of Lederle Laboratories.

Membership Now Open For Maine Physicians In Ohio's Two-Way Continuing Medical Education Seminars - - -

Applications are now being accepted for membership in the Ohio Medical Education Network (O-M-E-N), which begins its eighteenth year in mid-September. OMEN is the largest accredited, two-way, visually augmented, amplified telephone network for physicians in North America. During this past season, medical staffs at 126 hospitals in nine states and Canada took part in these unique Continuing Medical Education Seminars. While the programs originate "live" from the Ohio State University campus in Columbus, the conferences are actually held at participating hospitals, many of which are located hundreds of miles away.

and lasts one hour. One hour of Category 1 credit from the American Medical Association is available for attendance at each program. Continuing education study credit is also provided by the American Association of Family Physicians. The 1979-1980 season starts the week of September 17, 1979 and continues through the first week of May 1980 with "time off" during Thanksgiving week, Christmas week, and New Year's week.

The current long distance phone rates make this program no more costly for a physician or hospital in Maine or Florida than for a counterpart in many areas of Ohio.

Individuals wishing more complete information on the network are invited to call: 614-422-4985, or write:

Arthur A. Bartfay, Coordinator
The Ohio State University Center for CME
A-354 Starling Loving Hall
320 West Tenth Avenue
Columbus, Ohio 43210

Commission Of Pharmacy Reminds Pharmacists On Dispensing Non-approved Generics - - -

The Secretary of the State of Maine Commission of Pharmacy in June reminded pharmacists that there have been indications of shipment of "generic" pharmaceuticals into Maine which may have been manufactured by various pharmaceutical houses which have not received an NDA or ANDA from the Food and Drug Administration. Physicians in Maine who want to be certain that their patients are dispensed approved brand pharmaceuticals may check the box on their prescription blank whenever a questionable drug is being prescribed. Another alternative would be to call or write local pharmacists, expressing desires concerning brand name, generic, and non-approved generic drugs.

M.M.A. Augusta Headquarters One Step Nearer - - -

The decision of the House of Delegates to transfer MMA headquarters to Augusta, after many years in Brunswick, moved one step closer to implementation with the agreement to purchase a home on Western Avenue in Augusta. Renovations for additional parking and meeting space will be required but the building will provide modest office accommodations with convenient access to the Interstate. An optomistic timetable for the transfer is September.

Relative Value Guide For Anesthesiologists Permitted In District Court Ruling - - -

The Justice Department's suit against the American Society of Anesthesiologists, charging that the Society and its members conspired to fix fees through the use of relative value guides has resulted in a ruling favorable to the ASA. Judge Kevin Duffy ruled in a Federal District Court in Manhattan that "There is no evidence that the guides were intended as anything other than a suggested methodology for arriving at appropriate fees."

Similar charges in the past against state medical associations and specialty societies had resulted in consent decrees wherein those groups had agreed to terminate publication and distribution of their relative value guides.



CONTINUING MEDICAL EDUCATION IN MAINE

Conferences and Workshops

Title: **Management Systems for Hospital Cost Containment**
Date: August 16-18, 1979
Location: Shawmut Inn; Kennebunkport
Sponsors: Maine Hospital Association; Maine Voluntary Cost Containment Committee
For further information contact Margery Read; 622-4794

Title: **Strategies in Infectious Diseases**
Date: September 15, 1979
Location: Schaeffer Theatre-Bates College; Lewiston
Sponsors: St. Mary's General Hospital, Central Maine Medical Center, and Bates College
Credit: AMA Category I—6 hours; AAFP (elective)—6 hours
Reg. Fee: $10.00
For further information contact Michael C. Bach, M.D., Chief of Medicine, St. Mary's General Hospital; 783-2227

Title: **Family Medicine—Update**
Date: September 24-26, 1979
Location: Samoset Resort Inn, Rockport
Sponsor: Medical Care Development, Inc.
Credit: AMA Category I—15 hours; AAFP (prescribed)—15 hours
Reg. Fee: $150.00
For further information contact Gerald Goold; 622-7566

Programs Sponsored by Mid-Maine Medical Center/Colby College

Title: **Office Dermatology**
Date: July 29-August 2, 1979
Location: Colby College
Credit: AMA Category I—16 hours; AAFP (prescribed)—16 hours
Reg. Fee: $200.00

Title: **F.T. Hill Seminar in Otolaryngology**
Date: July 29-August 2, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—18 hours
Reg. Fee: $225.00

Title: **Ophthalmology Seminar**
Date: August 5-9, 1979
Location: Dean Auditorium, MMMC
Credit: AMA Category I—18 hours
Reg. Fee: $225.00

Title: **Topics in Clinical Nuclear Medicine**
Date: August 12-17, 1979
Location: Colby College
Credit: AMA Category I—30 hours
Reg. Fee: $350.00

Title: **Current Aspects of Obstetrics and Gynecology**
Date: August 12-16, 1979
Location: Colby College
Credit: AMA Category I—18 hours; AAFP (elective)—18 hours
Reg. Fee: $225.00

Title: **Continuing Topics in Forensic Sciences**
Date: August 19-23, 1979
Location: Colby College
Credit: AMA Category I—21 hours; AAFP (elective)—21 hours
Reg. Fee: $275.00

Title: **Topics in Pulmonary Disease**
Date: August 19-23, 1979
Location: Colby College
Credit: AMA Category I—19 hours
Reg. Fee: $240.00
For further information on all the programs sponsored by Mid-Maine Medical Center/Colby College, contact Robert H. Kany, Ph.D.; Division of Special Programs, Colby College, Waterville, Maine 04901; 873-1131

Hospital Activities

Augusta General Hospital
Augusta, Maine

August 28, 1979 **Ophthalmology Conference**
7:30-8:30 a.m. William E. Atlee, M.D., AGH
Robert Takach, M.D., MMC
Programs have been certified AMA Category I and AAFP (prescribed). For further information contact Mrs. Nancy York; 623-4711. Programs may be viewed over ITS.

Dean Hospital
Greenville, Maine

August 17, 1979 **Clinical Consultations—Oncology**
9:30 a.m.-Noon Eugene Beaupre, M.D., MMC
Programs have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621

Eastern Maine Medical Center
Bangor, Maine

Every Mon.	EEG Conference	12-1 p.m.
Every Mon.	Surgical Service—Chief's Rounds	5-6 p.m.
Every Tues.	Family Therapy Seminar	12-2 p.m.
2nd Tues.	Family Practice Service Meeting	6:30-7:30 p.m.
3rd Tues.	Dermatology-Pathology Conference	5-6 p.m.
3rd Tues.	Dermatology Section Meeting	6-7 p.m.
Every Wed.	Tumor Clinic Conference	2-5 p.m.
1st Wed.	Hematology/Oncology Meeting	8-9 a.m.
Every Thurs.	Psychiatric Continuing Education	10-11 a.m.
Every Thurs.	Pediatric Grand Rounds	9-10 a.m.
Every Thurs.	Cardiology Conference	11 a.m.-1 p.m.
1st Thurs.	Ophthalmology Section Meeting	7:30-8:30 a.m.
2nd Thurs.	Orthopedic Grand Rounds	7:45-8:45 a.m.
3rd Thurs.	GYN Analysis Conference	8-9 a.m.

4th Thurs.	Orthopedic Service Meeting	7:30-9 a.m.
4th Thurs.	Surgical Service Death Review	7:45-8:45 a.m.
4th Thurs.	Urology Section Conference	7:30-8:30 a.m.
Every Fri.	Neurology Grand Rounds	8-9 a.m.

All activities have been certified AMA Category I. For further information contact Robert H. Brown, M.D., Chairman, Med. Ed. Committee; 947-3711 Ext. 330.

Maine Medical Center
Portland, Maine

Every Mon.	Student Technologist Conference	8 a.m.
Every Mon.	Hematology Pathology Conference	11 a.m.
Every Mon.	Pulmonary Conference	12 Noon
Every Mon.	Pediatric Residents Conference	1 p.m.
Every Mon.	Anesthesia Formal Resident Lecture	3:30 p.m.
Every Mon.	Surgical Pathology Review	4 p.m.
Every Mon.	Radiology Journal Club	5 p.m.
1st & 3rd Mon.	Clinical Nephrology Conference	11 a.m.
1st & 3rd Mon.	Hematology-Pathology Conference	12 Noon
3rd Mon.	Eye Conference	11:45 a.m.
Every Tues.	Radiology Residents' Seminar	7 a.m.
Every Tues.	Family Practice Grand Rounds	9 a.m.
Every Tues.	Electrocardiographic Interpretation	1 p.m.
Every Tues.	Psychiatric Grand Rounds	1:30 p.m.
Every Tues.	Anesthesia Formal Resident Lecture	3:30 p.m.
Every Tues.	Surgical Seminar	4 p.m.
Every Tues.	Pathology Slide Seminar	4 p.m.
1st & 3rd Tues.	Radiology Pathology Conference	12 Noon
1st & 4th Tues.	Neurology Conference	12 Noon
2nd Tues.	Infectious Disease Conference	12 Noon
3rd Tues.	Hematology Conference	12 Noon
5th Tues.	Oncology Conference	12 Noon
Every Wed.	Radiation Therapy Conference	7 a.m.
Every Wed.	Urology Conference	7 a.m.
Every Wed.	Student Technologist Conference	8 a.m.
Every Wed.	Continuing Education Seminar	8 a.m.
Every Wed.	Medical Conference	9 a.m.
Every Wed.	Psychiatric Journal Club	12 Noon
Every Wed.	Cardiology Seminar	12 Noon
Every Wed.	Surgical Grand Rounds	5 p.m.
2nd Wed.	Guest Internist—Medical Conference	9 a.m.
4th Wed.	Medical Mortality Conference	9 a.m.
Alt. Wed.	Neurology-Psychiatry Seminar	11 a.m.
Alt. Wed.	Anesthesiology Journal Club	3 p.m.
Every Thurs.	Thoracic Surgery Conference	7 a.m.
Every Thurs.	OB/GYN Conference	7 a.m.
Every Thurs.	Anesthesiology Clinical Conference	7 a.m.
Every Thurs.	Diagnostic Radiology Teaching Conference	7 a.m.
Every Thurs.	Surgical Conference	8 a.m.
Every Thurs.	Pediatric Conference	9 a.m.
Every Thurs.	Tumor Consultation Board	11 a.m.
Every Thurs.	Medical Resident Conference	12 Noon
Every Thurs.	Surgical Seminar	4 p.m.
Every Thurs.	Endocrinology Conference	5 p.m.
Every Thurs.	Dental Specialty Lecture	6 p.m.
1st Thurs.	Anesthesia Mortality Conference	7 a.m.
1st Thurs.	Guest Pediatrician	9 a.m.
1st & 3rd Thurs.	Gastroenterology Conference	12 Noon
1st & 3rd Thurs.	Cardiac-Surgical Conference	12:30 p.m.
1st, 3rd, & 5th Thurs.	Pulmonary Physiology Conference	12:30 p.m.
2nd Thurs.	Cardiology Teaching Conference	12:30 p.m.
2nd Thurs.	Clinical Anesthesiology Lecture Series	3:30 p.m.
2nd Thurs.	Eye Staff Scientific Session	5:30 p.m.
2nd Thurs.	Maine Medical Center Medical Staff Meeting and Scientific Session	6 p.m.
2nd & 4th Thurs.	Pulmonary-Pathology Conference	12 Noon
2nd & 4th Thurs.	Endocrinology Conference	12 Noon
3rd Thurs.	Combined Guest Physician or Guest Surgeon Program	8 a.m.
3rd Thurs.	Clinical Anesthesiology Lecture Series	3:30 p.m.
4th Thurs.	Surgical Mortality Conference	8 a.m.
4th Thurs.	Anesthesia Mortality Conference	3:30 p.m.
Last Thurs.	Pediatric Mortality Conference	9 a.m.
Every Fri.	Thoracic Surgical Conference	7 a.m.
Every Fri.	Nuclear Medicine Conference	7 a.m.
Every Fri.	Student Technologist Conference	8 a.m.
Every Fri.	Neurological Neurosurgical Conference	8:30 a.m.
Every Fri.	Gastroenterology Conference	9 a.m.
Every Fri.	Medical Rehabilitation Staff Conf.	9 a.m.
Every Fri.	Orthopedic Conference	9 a.m.
1st Fri.	Dermatology Conference	12 Noon
2nd Fri.	Nephrology Conference	12 Noon
3rd Fri.	Rheumatology Conference	12 Noon
4th Fri.	Oncology Conference	12 Noon
Alt. Fri.	Oncology Radiation Conference	7 a.m.
Alt. Fri.	Gastroenterology Conference	10 a.m.

All programs have been certified AMA Category I. For further information contact Costas T. Lambrew, M.D.; 871-2111

Mid-Maine Medical Center
Waterville, Maine

July 26, 1979	**Rheumatology Series—Non-Articular Rheumatism** Currier McEwen, M.D., Regional Memorial Hospital
August 2, 1979	**Asplenia and Sepsis** Irvin Paradis, M.D., Samson Fisher, M.D., and David Ginder, M.D., MMMC
August 9, 1979	**Post-Operative Intensive Care of the Patient** Paul Levesque, M.D., Associate Professor of Anesthesiology, Tufts University School of Medicine
August 16, 1979	Program to be announced.
August 23, 1979	**Electrolyte Series—Salt and Water After Surgery** Richard Britton, M.D., MMC
August 30, 1979	Program to be announced.

All programs run from 12-1 p.m. and have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621. Programs may be viewed over ITS.

Redington Fairview Hospital
Skowhegan, Maine

July 25, 1979 12-1 p.m.	**Rheumatology Conference** Sidney Block, M.D., Eastern Maine Medical Center, Currier McEwen, M.D., Regional Memorial Hospital

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Eastern Maine Medical Center Issue

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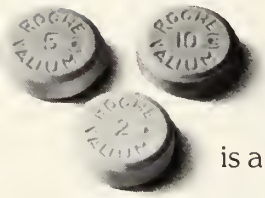
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***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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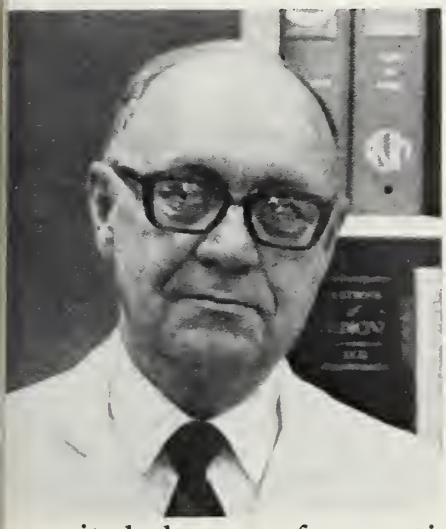
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PATIENT CARE Magazine—Outlook 1977, "Face-Off: Cost Containment vs. Chaos," January 1, 1977.

Lyle CB, et al. "Practice habits in a group of eight internists," ANNALS OF INTERNAL MEDICINE 84 (May 1976), 594-601.

Schroeder SA, et al. "Use of laboratory tests and pharmaceuticals: variation among physicians and effect of cost audit on subsequent use," JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 225 (Aug. 20, 1973), 969-73.

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Complete literature available on request from Professional Services Dept. PML.

The Journal
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Volume Seventy | Brunswick, Maine, August 1979 | Number 8

The Incidence and Prevalence of Coronary Heart Disease in Maine

Joe R. Wise, Jr., M.D.*

In the United States, cardiovascular diseases account for more deaths annually than all other causes combined. Last year more than 650,000 people died from myocardial infarction alone and it is estimated that 30,000,000 people suffer from some form of heart disease. In the next few years, as awareness of the serious nature and enormous scope of heart disease increases, the cost of caring for patients with heart disease can be expected to increase in a way that will seriously tax public and private resources. Unless some new means of treating or preventing this disease is discovered, this trend will certainly continue.

Physicians and medical facilities must plan to meet the needs of this large and growing number of patients with heart disease. To formulate these plans, some estimate of the number of patients requiring evaluation for heart disease is needed. The following study was undertaken to determine, using previously published population studies, the number of patients in a six county area of Northeastern Maine who might have some form of coronary heart disease requiring evaluation and treatment.

Deaths From Coronary Heart Disease

In Maine, the crude death rate from all heart disease is somewhat higher than in the U.S.: 3.82/1,000 population versus 3.37/1,000 in 1976.[1] This could well be due to the higher percent of elderly in Maine. Deaths from all heart disease decreased 6% from 1973 to 1976 in the State, and 6.6% in Northeastern Maine, including Aroostook, Hancock, Penobscot, Piscataquis, Waldo and Washington counties. For the two principal categories of CHD deaths, however, the picture was somewhat different. From 1973 to 1976, myocardial infarction (MI) deaths decreased 10% in the State and 6% in Northeastern Maine; chronic ischemic heart disease deaths decreased by 5% in the State but remained unchanged in Northeastern Maine[2] (Appendix A-C).

The Maine 1976 age-specific death rates for both MI and CIHD were applied to the six counties in Northeastern Maine using the broad age groups available for county population estimates: 18-44, 45-64 and 65+[3] (Appendix D). Actual MI deaths by

Appendix A

Deaths from Acute Myocardial Infarction
Maine, By Age and Sex, 1973-1977

Males					
Age Group	*1973*	*1974*	*1975*	*1976*	*1977*
20-24	0	1	0	0	0
25-34	4	6	5	2	5
35-44	38	42	32	35	30
45-54	139	166	161	133	141
55-59	170	144	157	114	137
60-64	206	182	180	187	173
65-69	229	254	237	210	201
70-74	241	207	203	212	202
75-79	201	206	186	174	199
80-84	171	139	139	146	120
85+	119	128	139	113	110
Total	1518	1475	1439	1326	1318
Females					
20-24	0	0	0	0	0
25-34	2	1	1	0	1
35-44	9	9	4	3	6
45-54	48	33	35	34	32
54-59	48	47	59	32	41
60-64	80	66	74	83	50
65-69	94	116	101	106	99
70-74	142	135	134	140	149
75-79	166	176	149	149	164
80-84	168	141	141	147	136
85+	173	174	161	178	200
Total	930	898	859	877	878
TOTAL, Both Sexes	2448	2373	2298	2203	2196

*From Cardiology Section, Medical Service, Eastern Maine Medical Center, Bangor, Maine 04401.

Appendix B

Deaths from Chronic Ischemic Heart Disease Maine, By Age and Sex, 1973-1977

Males					
Age Group	*1973*	*1974*	*1975*	*1976*	*1977*
20-24	0	1	1	0	1
25-34	0	0	1	1	1
35-44	5	5	7	3	5
45-54	19	20	29	37	30
55-59	32	41	23	31	42
60-64	44	42	38	53	45
65-69	67	67	69	79	73
70-74	97	94	95	106	111
75-79	125	126	114	112	107
80-84	150	129	136	116	108
85+	189	208	160	168	186
Total	728	733	673	706	709
Females					
20-24	0	0	0	0	0
25-34	0	0	0	0	0
35-44	0	2	0	2	2
45-54	4	6	8	9	6
55-59	12	19	7	7	14
60-64	19	21	19	21	20
65-99	45	44	41	44	43
70-74	78	68	88	76	68
75-79	137	104	127	132	113
80-84	171	186	162	154	161
85+	329	304	327	342	309
Total	795	754	780	787	736
TOTAL, Both Sexes	1523	1487	1453	1493	1445

county were lower or the same as predicted in Penobscot, Piscataquis, and Waldo counties; but higher by 15% in Hancock and by 25% in Aroostook and Washington counties. The higher percentage of elderly in Hancock and Washington counties could explain these counties' greater than expected number of deaths. (As age-specific death rates are quite high over age 65, the use of one death rate for the entire group may underestimate total deaths.) However, Piscataquis County also has a high proportion of elderly and no greater than expected number of MI deaths. Aroostook County has the youngest population in our area, and 25% more MI deaths than expected.

CIHD deaths were predicted for Northeastern Maine using the same method as for MI deaths. CIHD deaths were closer to the predicted number for most counties, but were still 22% higher than expected in Washington County (Appendix E).

Studies have shown that cause of death on death certificates is unreliable. Specifically, a study of deaths from arteriosclerotic heart disease in Baltimore revealed a 20% overestimate in ASHD deaths in the white population and a 30-50% overestimate in the black.[4] Area differences in assigning deaths to MI or CIHD may account for the differences in death rates seen with Northeastern Maine.

Incidence Of Symptomatic Coronary Heart Disease

Estimates of patients who would be likely to be

Appendix C

Acute Myocardial Infarction Deaths EMMC Service Area — 1973-1977

	Acute Myocardial Infarction Deaths				
County	*1973*	*1974*	*1975*	*1976*	*1977*
Aroostook	206	169	184	203	206
Hancock	95	93	93	107	86
Penobscot	270	231	268	230	244
Piscataquis	57	52	53	39	29
Waldo	50	48	42	47	64
Washington	105	105	117	96	104
Total	783	698	757	722	733

Chronic Ischemic Heart Disease Deaths EMMC Service Area — 1973-1977

	CIHD Deaths				
County	*1973*	*1974*	*1975*	*1976*	*1977*
Aroostook	92	96	85	100	80
Hancock	74	62	67	62	79
Penobscot	168	158	160	153	142
Piscataquis	22	15	13	24	23
Waldo	18	35	26	26	32
Washington	64	46	68	68	75
Total	438	412	419	433	431

evaluated for coronary heart disease in Northeastern Maine can be based upon reported studies giving the number of patients likely to come to the attention of a physician for CHD, number of persons dying from CIHD with history of heart disease, and the prevalence data for CHD.

The number of patients aged 35-64 who are likely to come to the attention of a physician for evaluation of CHD can be based on estimates of the incidence of angina without prior heart disease, the incidence of survivors of MIs, and the incidence of possible MIs.

Incidence Of Angina Without Prior Heart Disease

The incidence of angina was reported in both the HIP[5] and Framingham[6] studies. The HIP study showed a slightly lower incidence of angina, probably as all subjects in the study were currently employed. Applying HIP age-specific incidence of angina to the 1976 Maine population 35-64 thus results in a conservative estimate of 475 new angina patients.

Age	*Rate Angina/1,000*	*Population Maine 1976*	*Estimated New Angina Patients*	
Males				
35-44	0.46	51,300	23.6	
45-54	2.10	52,300	109.8	
55-64	3.93	45,900	180.4	313.8 males
Females				
35-44	0.11	53,900	5.9	
45-54	0.80	56,300	45.0	
55-64	2.16	51,200	110.6	161.5 females
			Total	475.3

Incidence Of MI Survivors

For estimates, MI survivors were considered to be exclusive of the group of patients with newly diagnosed angina although there is some overlap.

Appendix D

Acute Myocardial Infarction Deaths Per 1000 Population Maine, 1973 and 1978, By Age and Sex

Age Group	Myocardial Infarction Deaths/1,000 Population Males 1973	Males 1977	Females 1973	Females 1977
20-24	0.00	0.00	0.00	0.00
25-34	0.06	0.07	0.03	0.01
35-44	0.73	0.58	0.17	0.11
45-54	2.68	2.61	0.85	0.55
55-59	7.39	5.27	1.80	1.44
60-64	9.90	7.72	3.27	1.95
65-69	13.01	10.20	3.90	4.09
70-74	18.40	14.13	7.32	7.64
75-79	22.33	19.70	10.51	10.19
80-84	32.26	20.00	15.85	12.48
85+	34.00	26.83	20.12	22.73
Total	3.00	2.50	1.69	1.57

Source: *Population Estimates:* State Planning Office Statistical Reports, Population Projection Series PPS-3. August 1978.

Deaths: Maine Vital Statistics, Maine Department of Human Services, 1976. 1977 Data by Telephone.

Seventy-seven percent of patients having MIs in the Framingham study did not have prior angina.[7] Of those with angina, few would have had new angina (HIP study showed 12% of patients with new angina had an MI in a 30 month study.[8])

Rates of 1st MI were similar in the HIP and Framingham studies. Applying HIP age-specific incidence rates to the Maine population aged 35-64 gives an estimated 1,004 MIs in 1976.

Age	HIP-MIs/ 1,000	Population Maine 1976	Estimated Incidence MIs, ME
Males			
35-44	1.55	51,300	79.50
45-54	5.72	52,300	299.16
55-64	9.67	45,900	443.85
Females			
35-44	0.05	53,900	2.70
45-54	0.61	56,300	34.34
55-64	2.82	51,200	144.67
			Total 1004.22

It may be valid at this time to include the incidence of all MIs, not just the first. Patients treated conservatively for an MI several years ago may now be considered for surgery. The Nashville study included all MIs not just the first.[9] Using the incidence rates from this study, 1555 MIs would be predicted in Maine in 1976.

Age	HIP-MIs/ 1,000	Population Maine 1976	Estimated Incidence MIs, ME
Males			
35-44	2.34	51,300	120.04
45-54	6.81	52,300	356.16
55-64	14.65	45,900	672.44
Females			
35-44	2.04	53,900	109.96
45-54	1.43	56,300	80.51
55-64	4.22	51,200	216.06
			Total 1555.17

Appendix E

Chronic Ischemic Heart Disease Deaths/1000 Population Maine, 1973 and 1978, By Age and Sex

Age Group	CIHD Deaths/1000 Population Males 1973	Males 1977	Females 1973	Females 1977
20-24	0.00	0.02	0.00	0.00
25-34	0.00	0.01	0.00	0.00
35-44	0.10	0.10	0.00	0.04
45-54	0.37	0.55	0.07	0.10
55-59	1.39	1.62	0.45	0.49
60-64	2.12	2.01	0.78	0.78
65-69	3.81	3.71	1.87	1.78
70-74	7.40	7.76	4.02	3.49
75-79	13.89	10.59	8.67	7.02
80-84	28.30	18.00	16.13	14.77
85+	54.00	45.37	38.26	35.11
Total	1.44	1.34	1.44	1.32

In the Framingham study, 35% of MI patients died within the first weeks of their attack.[10] Using this death rate, and the estimated number of MIs in Maine (1976):

Estimated first MIs 1004.22 x 0.65 = 652 survivors
Estimated total MIs 1555.17 x 0.65 = 1011 survivors

Estimated deaths from all MIs of persons 35-64 were 544 (1555 x 0.35). This is somewhat less than the 621 deaths from MIs in this age group reported in Maine in 1976. As mentioned before, this diagnosis is apt to be overreported—if 10% were in fact not MI deaths, this would leave 559 with the diagnosis.

Incidence of Possible MIs

Most studies of the incidence of CHD include a borderline category of possible or probable disease. HIP incidence rates applied to the Maine population 35-64 give an estimated 295 possible MIs/year.

Age	Possible MIs/1,000	Population Maine 1976	Estimated Possible MIs
Males			
35-44	0.24	51,300	12.31
45-54	1.10	52,300	57.53
55-64	2.52	45,900	115.67
Females			
35-44	0.07	53,900	3.77
45-54	0.54	56,300	30.40
55-64	1.48	51,200	75.78
			Total 295.46

Summary: The number of patients in Maine aged 35-64 likely to come to the attention of a physician for evaluation of CHD in 1976:

- 475 new angina patients/yr
- 652 survivors of first MI (or 1,011 survivors of any MI/yr)
- 295 patients having possible MI/yr
- 1422 patients between ages 35-64 (or 1781 if include survivors of any MI)

Appendix F

MI Deaths in EMMC Service Area Predicted (Using State MI Death Rate) Versus Actual, 1976

1. Maine MI Death Rates, 1976.

Age Group	*Deaths, MI*	*Estimated Population 1976*	*Deaths MI/ 1,000 Population*
18-44	40	391,078	0.10
45-64	583	205,642	2.84
65 +	1575	131,762	11.95

2. Predicted MI Deaths By County.

	Aroostook	*Hancock*	*Penobscot*	*Piscataquis*	*Waldo*	*Washington*
Population 18-44	38,258	13,817	54,358	5,697	10,199	11,796
MI Deaths/1000	0.10	0.10	0.10	0.10	0.10	0.10
Predicted Deaths	3.82	1.38	5.44	0.57	1.02	1.18
Population 45-64	16,909	7,646	24,339	3,591	4,789	6,366
MI Deaths/1000	2.84	2.84	2.84	2.84	2.84	2.84
Predicted Deaths	48.02	21.71	69.12	10.20	13.60	18.08
Population 65 +	9,307	5,809	14,198	2,520	3,037	4,902
MI Deaths/1000	11.95	11.95	11.95	11.95	11.95	11.95
Predicted Deaths	111.22	69.42	169.67	30.11	36.29	58.56
Total Predicted MI Deaths	163.06	92.51	244.23	40.88	50.91	77.82
Actual MI Deaths, 1976	203	107	230	39	47	96
Ratio Population 65 + to 18-44	.24	.42	.26	.44	.30	.42

Appendix G

Chronic Ischemic Heart Disease (CIHD) Deaths in EMMC Service Area Predicted (Using State CIHD Death Rate) Versus Actual, 1976

1. Maine CIHD Death Rates, 1976.

Age Group	CIHD *Deaths*	*Population 1976*	*CIHD Deaths 1,000 Population*
18-44	6	391,078	0.02
45-64	158	205,642	0.77
65 +	1329	131,762	10.09

2. Predicted CIHD Deaths By County.

	Aroostook	*Hancock*	*Penobscot*	*Piscataquis*	*Waldo*	*Washington*
Population 18-44	38,258	13,817	54,358	5,697	10,199	11,796
CIHD Deaths/1000	0.02	0.02	0.02	0.02	0.02	0.02
Predicted Deaths	0.77	0.28	1.09	0.11	0.20	0.24
Population 45-64	16,909	7,646	24,339	3,591	4,789	6,366
CIHD Deaths/1000	0.77	0.77	0.77	0.77	0.77	0.77
Predicted Deaths	13.01	5.89	18.74	2.77	3.69	4.90
Population 65 +	9,307	5,809	14,198	2,520	3,037	4,902
CIHD Deaths/1000	10.09	10.09	10.09	10.09	10.09	10.09
Predicted Deaths	93.93	58.61	143.25	25.42	30.64	49.46
Total Predicted CIHD Deaths	107.71	64.78	163.08	28.30	34.53	54.60
Actual CIHD Deaths	100	62	153	24	26	68

Northeastern Maine

State rate is 4.57/1,000 (1422/310900) or 5.73/1,000 if include survivors of any MI. (Incidence per year for population 35-64)

The 1976 population estimate for Northeastern Maine six county area is 96,219 for ages 35-64. Estimated State rates applied to this give an estimated 440 CHD patients in Northeastern Maine or 550 if survivors of all MIs were included.

Population Aged 65-74

These estimates can be expanded to include those 65-74 years of age by 5 or 10 years. Information is scanty,[19] but a conservative estimate would be to use the incidence rates of the 55-64 year group for those age 65-74. This would add 226 new angina patients,

PROJECTED MYOCARDIAL INFARCTION DEATHS
MAINE, 1985

Males	*Projected Population*	*1977 Age-Specific Death Rate/1000 for MI*	*Projected 1985 MI Deaths*
20-24	53,000	0.00	0.00
25-34	101,100	0.07	7.08
35-44	68,000	0.58	39.44
45-54	50,800	2.61	132.59
55-59	26,300	5.27	138.60
60-64	25,600	7.72	197.63
65-69	22,400	10.20	228.48
70-74	15,500	14.13	219.02
75-79	11,800	19.70	232.46
80-84	7,300	20.00	146.00
85+	5,200	26.83	139.52
Total	567,000		1480.82
Females			
20-24	53,500	0.00	0.00
25-34	101,800	0.01	1.02
35-44	71,400	0.11	7.85
45-54	54,700	0.55	30.09
55-59	28,800	1.44	41.47
60-64	29,200	1.95	56.94
65-69	27,600	4.09	112.88
70-74	21,200	7.64	161.97
75-79	18,800	10.19	191.76
80-84	13,100	12.48	163.49
85+	11,300	22.73	256.85
Total	603,700		1024.32
Both Sexes			2505.14

291 MI survivors of 1st MIs (assuming survival rates are the same), and 153 possible MIs: a total of 670 additional patients in the State or 208 in Northeastern Maine (or 254 more in Northeastern Maine if survivors of all MIs are considered).

Estimates Projected To 1990 For Northeastern Maine

The 1976 estimates can be projected to 1995, assuming the ratio of Northeastern Maine service area population to total state population would not change. (Age-specific rates of CHD events held constant.)

Age Group	*New CHD*			*New CHD & Survivors of Second or Later MI*		
	1976	*1985*	*1995*	*1976*	*1985*	*1995*
35-64	440	500	630	550	630	795
65-74	208	234	296	254	286	361
35-74	648	734	926	804	916	1,156

Estimated Incidence Of CHD Using Mortality Data

Another way to approach the estimate of patients who have CHD is to focus on those persons who actually die from coronary disease. Using 1976 data, and ages 35-64, there were 784 deaths in the State from MI or CIHD, or an estimated 243 in Northeastern Maine.

Using these deaths alone underestimates the possible patient pool as patients with treatable coronary disease may die from other causes. An underestimate also results within the 35-64 year age group as patients with newly diagnosed CHD in their fifties may die from the disease after age 65. Few with CHD under 35 would contribute to deaths in the 35-64 year age group.

One source of an overestimate would be the tendency to overreport CHD deaths. Another source of an inflated estimate occurs as many persons who die suddenly from CHD have no prior history of heart disease; these persons would never reach the potential patient pool with existing patient behavior and medical technology.

An estimate of patients per year who may enter the group would include:

—Deaths from MI & CIHD, ages 35-74 (1976):	1435
—Increased by 25% to estimate deaths from other causes:	1794
—Decreased by 50% to estimate those likely to seek medical care for CHD:	897
—Decreased by 31% to estimate those in Northeastern Me.:	278

The estimate of 278 is understandably less than the 440 estimated using incidence of CHD events as it would not include those with angina, nor those with less severe or questionable disease.

Prevalence of Coronary Heart Disease

Information available so far on the prevalence of CHD is slim; one reference to the prevalence of angina found at the beginning of the Framingham

study[8] and the National Health Survey of heart disease in 1960-62.[11]

Prevalence of angina in the Framingham study was noted in Weinblatt (et al's) follow-up of HIP angina patients.[8] Using Weinblatt's numbers, prevalence of angina in the Framingham population age 30-62 was 4%. This would mean that there were 12,436 persons in Maine with angina. Age-specific incidence of angina (used above) held constant over 30 years gives only 8,640 persons with angina between 35 and 64 in Maine—if no one died between ages 35-64.

The high prevalence of angina in Framingham could be the result of (a) overdiagnosis to avoid including anyone with existing heart disease in the original study group and (b) self-selection within the Framingham population volunteering for the study of those persons with existing chest pain.

In 1960-62, 6,672 persons from 18-79 years old were examined in a National Health Survey of heart disease.[11] Age-specific prevalence rates (from the study) of CHD applied to the 1976 Maine population gives 18,872 persons 35-64 with CHD—or 6.1% of that population. Of the total with CHD, 10,266 (3.3%) were thought to have definite CHD and 8,606 (2.8%) suspected CHD.

Estimated Prevalence of CHD, Maine 1976

	*Percent with CHD**		*1976 Maine Population (000's)*	*Estimated Population in Maine With CHD*		
	Definite	*Suspected*		*Definite*	*Suspected*	*Total*
Males						
35-44	1.2%	1.0%	51.3	615.6	513.0	1,128.6
45-54	3.0	3.5	52.3	1,569.0	1,830.5	3,399.5
55-64	10.3	4.2	45.9	4,727.7	1,927.8	6,655.5
Females						
35-44	0.4	0.5	53.9	215.6	269.5	485.1
45-44	1.3	2.4	56.3	731.9	1,351.2	2,083.1
55-64	4.7	5.3	51.2	2,406.4	2,713.6	5,120.0
Total				10,266.2	8,605.6	18,871.8

Prevalence of CHD in Maine using the National Health Survey rates are curiously close to a rough estimate made using incidence estimates derived above. The rough estimate of prevalence was made by assuming that the mortality rate of persons with angina, survivors of first MIs and those with possible MIs were equal to that of angina patients: i.e., 4%/year. The 1976 Maine population was used, disregarding population change over time—i.e., the estimated number of persons in each sex/age group was used rather than rates. Prevalence of CHD estimated this way was 17,964, compared to the 18,872 found using National Health Survey rates. Thus, it appears that the incidence estimates above are at least good approximations.

The data on the incidence of CHD presented above suggests that in Maine 1781 persons between the ages of 35 and 64 develops CHD each year, or 550 patients annually in this age group for the six county area of Northeastern Maine. These figures could be expected to increase to 2032 and 630 for Maine and Northeastern Maine respectively by 1985. The number of patients in this age group in Maine estimated to already have some form of CHD is 18,871.

Summary

Using previously published population studies the incidence and prevalence of coronary heart disease applied to the age-specific population in Maine for 1976 it can be estimated that there are approximately 18,871 people between the ages of 35 and 64 in Maine who now have some form of coronary heart disease with 1,781 new cases appearing annually. These numbers can be expected to increase by 15% by 1985 and even more if those over age 64 are included.

Improved medical and surgical treatment have been very effective in relieving the disabling symptoms of many and prolonging the life of some patients with coronary heart disease. These recent advances have been spectacular and have probably contributed to the 30% decline in death rate from cardiovascular disease which has occurred during the last 30 years, with the most dramatic decline (15%) occurring in the past 5 years. Further improvements in medical and surgical treatment now under development may have even greater beneficial effect.

Facilities must be provided in the State to insure for these patients the kind of treatment now available and that which may be developed in the future. This effort will involve screening a very large number of people suspected of having coronary heart disease.

It is apparent from considering the figures above, the serious nature and wide prevalence of coronary heart disease in our population. Efforts to provide the care required by this large number of patients can be expected to seriously tax our public and private resources. The cost of providing this care will be offset to some extent by the income produced by those patients now disabled by remediable heart disease who are, as a result of this care, able to return to work. Plans should be made now to insure that the recent and future advances in the care of coronary heart disease be made readily available to all those in Maine who require it. In formulating these plans, it will be important to consider, from the financial point of view, not only the expense of treating those patients with coronary heart disease, but also the alternate expense to society of subsidizing those who

Continued on Page 312

Evaluation and Management of Mitral Valve Disease*

Joe R. Wise, Jr., M.D.**

The mitral valve is a complex apparatus, more than just a door, composed of, in addition to leaflets, the mitral valve annulus, the chordae, the papillary muscles and the wall of the left ventricle which serves to anchor the papillary muscles. Proper function of the mitral valve requires a coordinated and properly timed function of all of these integral parts to prevent eversion of the mitral valve into the left atrium during systole, while subjected to the highest pressure gradient in the circulation.[1]

In general, the mitral valve can malfunction in two ways—it can be stenotic or regurgitant. These two types of malfunction have distinctly separate clinical pictures and require different treatment.

Mitral Stenosis

Mitral valve obstruction may be either congenital or rheumatic. Congenital mitral stenosis is unusual in adults and rheumatic fever is by far the most common cause. As a result of rheumatic fever, the mitral valve leaflets are thickened and sometimes calcified. The commissures are fused, the chordae are thickened and fused converting the orifice of the mitral valve into a funnel-like narrowing.

The hemodynamic consequences of mitral stenosis do not become manifest clinically until the orifice is narrowed by about one-half. At that point, the stenosis produces a resistance to flow and flow into the left ventricle becomes turbulent. To maintain left ventricular filling, the left atrial pressure must rise. The left atrial pressure, therefore, is a function of not only mitral valve orifice size, but also the length of the diastolic filling period, which in turn is determined by the heart rate.

When sinus rhythm is present, left ventricular filling remains near normal since augmented left atrial systole keeps flow normal. With time, atrial fibrillation develops, left atrial systole is lost, left atrial pressure rises, cardiac output falls and sluggish left atrial flow predisposes to clot formation.

The immediate consequence of increased left atrial pressure is pulmonary venous congestion with pulmonary edema. Decreased lung compliance increases the work of breathing which is manifest as dyspnea. The shortness of breath is aggravated by exercise which increases the venous return and increases the heart rate, shortening diastolic filling time. If mitral stenosis is severe, pulmonary hypertension develops with resultant right ventricular hypertrophy, congestive heart failure, tricuspid regurgitation and pulmonic regurgitation.

Symptoms

Symptoms are related to the severity of the mitral stenosis and dyspnea is the most prominent feature. Initially, with mild stenosis, dyspnea may occur only with exertion. There may be nocturnal cough or paroxysmal nocturnal dyspnea. Palpitations are frequent, usually atrial ectopic beats or paroxysmal atrial fibrillation. During this early period, the risk of embolism is high and may be the presenting symptom in 10% to 15% of patients.[2,3] Hemoptysis may occur due to rupture of bronchial vessels or pulmonary edema. With the development of pulmonary hypertension, right heart failure may result with relief from the dyspnea at the expense of low cardiac output and fatigue.

Physical Signs

The murmur of mitral stenosis is characteristic; it is diastolic, low-pitched and heard best with the bell of the stethoscope in the left lateral decubitus position. The duration of the murmur in diastole is related to the severity of the stenosis and may extend throughout the length of diastole. The intensity of the murmur and the duration of the murmur are increased following exercise. If the valve is pliable, the first heart sound is loud and an opening snap is present, usually best heard low along the left sternal edge, rather than at the apex about 0.10 seconds after aortic valve closure. If the stenosis is severe and the left atrial pressure high, the mitral valve is "snapped open" very early in diastole soon after the aortic valve closure sound. The more severe the stenosis the earlier the opening snap occurs after the second heart sound. With calcification of the mitral valve, the valve becomes regurgitant, and the loud first heart sound and opening snap are lost and replaced by the murmur of mitral regurgitation and a third heart sound. Thus the physical signs of mitral stenosis, reflect not only the severity of the stenosis, but also the pliability of the valve and the suitability for valvotomy.

There may be signs of pulmonary hypertension with a right ventricular heave, a loud pulmonic valve closure sound and an early diastolic murmur of pulmonic regurgitation along the left sternal edge. The left ventricular impulse in mitral stenosis is not usually palpable and, if so, requires an explanation. A palpable left ventricular impulse in this circumstance suggests associated left ventricular hypertrophy due to related aortic valve disease or mitral regurgitation or left ventricular hypertrophy from

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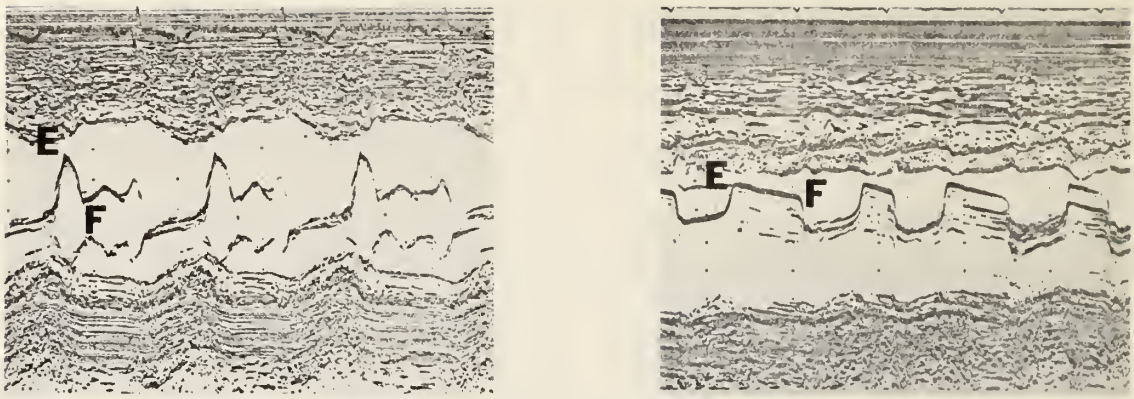


Fig. 1. Echocardiogram showing movement of mitral valve of normal patient (left) and patient with mitral stenosis (right). The diastolic closure rate (E-F) of the anterior mitral valve leaflet is markedly reduced when mitral stenosis is present.

some other cause such as hypertension.

The electrocardiogram is normal early in the course of mitral stenosis and relatively insensitive. With more severe mitral stenosis, the P wave may be abnormal, reflecting left atrial hypertrophy, and there may be signs of right ventricular hypertrophy. Left ventricular hypertrophy is absent. The chest x-ray in well developed mitral stenosis characteristically shows left atrial enlargement with prominence of the upper lobe pulmonary veins (so called "cephalization"). Calcium may be detected within the mitral valve usually more readily appreciated with flouroscopy and, in severe cases, there may be signs of pulmonary hypertension with enlargement of the pulmonary artery and right ventricle.

The echocardiogram is very helpful in confirming the presence and severity of mitral stenosis (Figure 1). The evaluation of the mitral valve was one of the earliest applications of echocardiography.[4] In diastole, the normal mitral valve opens widely then floats back to a more neutral position and is then reopened widely by atrial systole producing a characteristic "M shaped" motion. When mitral stenosis is present, the mitral valve is held widely open during diastole by the torrent of blood through the stenotic valve and the diastolic closure rate is markedly reduced. In contrast to the normal valve, the posterior mitral valve leaflet and the anterior leaflet move forward as a unit since they are bound together. The amplitude of anterior leaflet movement is a reflection of the mobility of the valve and thickened or calcified leaflets produce denser echos. The size of the left atrium can also be evaluated.[5]

Natural History

Clinical mitral stenosis may occur as early as two years after acute rheumatic fever. Usually mitral stenosis requires ten years to develop and twenty years to become symptomatic.[6] The interval from the onset of symptoms to total disability averages seven years[7] and 50% of Class III patients are dead within six years.[6] Progression of the mitral valve obstruction can occur in the absence of clinical evidence of rheumatic activity.

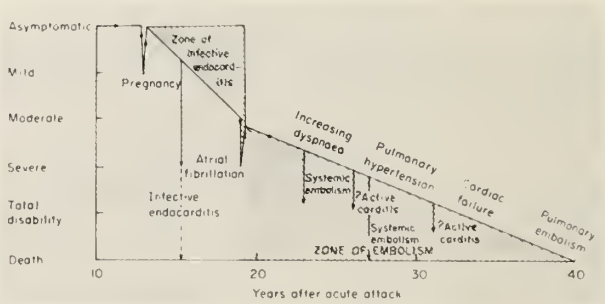


Fig. 2. The natural history of rheumatic mitral stenosis. From Goodwin, J.F. (1969), *Medical* and *Surgical Cardiology*, p. 846, Blackwell Scientific Publication; by permission of the author and publisher.

Early in the course of mitral stenosis symptoms occur only with pregnancy or during exertion or with the onset of atrial fibrillation (Figure 2). After the onset of atrial fibrillation, there is a gradual progressive increase in dyspnea, with the eventual appearance of pulmonary hypertension, congestive heart failure and decreased cardiac output. Systemic embolism occurs in 30% of patients with mitral stenosis during their lifetime,[2] and is the first symptom in 10% to 15%.[3]

Management

Rheumatic fever prophylaxis should be initiated as soon as the diagnosis of mitral stenosis is made. Although recurrent attacks of rheumatic fever occur at any age, the risk of recurrence decreases with age. Individuals with high risk of exposure to streptococcal infection include young men in military service, parents of young children, school teachers, physicians, nurses and medical personnel. Individuals with high recurrence rates for rheumatic fever per infection are those with rheumatic heart disease, those with a previous attack of rheumatic fever, or those with multiple attacks. The risk of acquiring a streptococcal infection and the possibility of recurrent attacks of rheumatic fever continue throughout life

Continued on Page 307



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Pale green 300 mg. tablets
in bottles of 100 and Single Unit Packages of 100
(intended for institutional use only).
Injection, 300 mg./2 ml.,
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SK&F LAB CO.
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When painful spasm is the presenting symptom . . .



...in the functional bowel/irritable bowel syndrome*

Bentyl®

(dicyclomine hydrochloride USP)

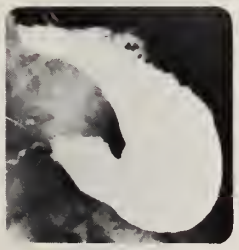
10 mg. capsules, 20 mg. tablets,
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helps control abnormal motor activity
with minimal anticholinergic side effects†

Demonstrated smooth muscle relaxant activity.

In this double-blind study, twenty patients having G.I. series and exhibiting spasm were randomly selected to receive either 2 cc. of Bentyl or sodium chloride intramuscularly. Ten minutes after the injection another radiograph was taken . . .

. . . Bentyl produced definite relaxation in 8 of 10 patients. The sodium chloride produced relaxation in only 3 of 10. No side effects occurred in either group of patients.



Pylorospasm has almost totally blocked passage of barium meal.



Barium meal beginning to pass 10 minutes after intramuscular injection of 20 mg. Bentyl.

"The correlation of spasm relief and drug given was excellent."

*This drug has been classified "probably" effective in treating functional bowel/irritable bowel syndrome.

†See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964.

Merrell

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Bentyl®

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Brief Summary

INDICATIONS

Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the following indications as "probably" effective:

For the treatment of functional bowel/irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

THESE FUNCTIONAL DISORDERS ARE OFTEN RELIEVED BY VARYING COMBINATIONS OF SEDATIVE, REASSURANCE, PHYSICIAN INTEREST, AMELIORATION OF ENVIRONMENTAL FACTORS.

For use in the treatment of infant colic (syrup).

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient; unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: Autonomic neuropathy. Hepatic or renal disease. Ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension. Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia; urinary hesitancy and retention; blurred vision and tachycardia; palpitations; mydriasis; cycloplegia; increased ocular tension; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea, vomiting, impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs.

Usual Dosage: Bentyl 10 mg. capsule and syrup: *Adults*: 1 or 2 capsules or teaspoonfuls syrup three or four times daily. *Children*: 1 capsule or teaspoonful syrup three or four times daily. *Infants*: ½ teaspoonful syrup three or four times daily. (May be diluted with equal volume of water.) Bentyl 20 mg.: *Adults*: 1 tablet three or four times daily. Bentyl Injection: *Adults*: 2 ml. (20 mg.) every four to six hours intramuscularly only. NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE: The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

Product Information as of October, 1978.

Injectable dosage forms manufactured by CONNAUGHT LABORATORIES, INC., Swiftwater, Pennsylvania 18370 or TAYLOR PHARMACAL COMPANY, Decatur, Illinois 62525 for MERRELL-NATIONAL LABORATORIES, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215, U.S.A.

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and it is therefore suggested that the safest general procedure is to continue the rheumatic fever prophylaxis indefinitely. Some physicians may wish to make exceptions in certain of their adult patients, but before exceptions are made, the physician should carefully weigh the risks of acquiring streptococcal infection as well as the recurrence rate of rheumatic fever per infection, and the consequence of recurrence. The monthly intramuscular injection of benzinthine penicillin G (1.2 million units per month) is the method of choice for rheumatic fever prophylaxis since it is considerably more effective than oral methods. Alternate methods include the oral administration of buffered penicillin G (200,000 to 250,000 units, once or twice daily) or, for the exceptional patient who may be sensitive to pencillin, oral sulfadizine (1 gm. once daily). Long acting sulfadizine should be avoided because of the high incidence of side effects. Tetracycline should not be used because of the high number of strains of streptococci resistant to this antibiotic.[8]

Prophylaxis for infective endocarditis should be used in conjunction with dental manipulator, oral surgery, bronchoscopy, instrumentation of the genitourinary tract, surgery of the lower intestinal tract and childbirth.[9]

Antiarrhythmic agents such as digitalis or propranolol may be required to control the paroxysmal atrial rhythm disturbances or the ventricular response in established atrial fibrillation. Diuretics may be helpful in controlling the pulmonary venous congestion and peripheral edema in patients for whom surgery is not suitable.

The preferred treatment for symptomatic mitral stenosis is surgical relief of the mitral valve obstruction. If the valve is pliable and no mitral regurgitation is present, a mitral valvotomy can be performed with a mortality risk in the range of 1% and can provide palliative symptomatic relief for many years. For those patients with disabling symptoms and a valve that is unsuitable for valvotomy, mitral valve replacement is required.

Systemic Embolism[2,3]

The risk of systemic embolism increases with the appearance of atrial fibrillation and varies from 8% in patients with mitral stenosis and normal sinus rhythm to 30% in those with atrial fibrillation. The incidence of atrial fibrillation is related to the age of the patient and the presence of mitral valve calcification, but is not related to the severity of the symptoms. Systemic embolism may be the first symptom in 10% to 15% of patients with mitral stenosis and 75% of the time the embolus is cerebral. In 20% of patients the embolism occurs when sinus rhythm is present. One-third of emboli occur within one month of the onset of atrial fibrillation and two-thirds within twelve months. The mortality of the first embolus is in the range of 7%, further embolism is likely in over half of these patients and the mortality of a recurrent embolism is 27%. The patients at high risk of embolism are difficult to identify. Twenty percent (20%) are in sinus rhythm at the time of the embolus and the incidence of embolism is not related to the left atrial size or the severity of the symptoms.

Patients with more than minimal mitral stenosis should receive anticoagulants. With the onset of atrial fibrillation, valvotomy should be considered if the valve is suitable since this has been shown to decrease the risk of embolism.[3] If the valve is unsuitable for valvotomy, anticoagulants should be continued and, if symptoms indicate, the mitral valve replaced.

Mitral Regurgitation

Normal mitral valve function requires a coordinated function of the leaflets, the papillary muscles and the cordae to keep the leaflets from prolapsing into the left atrium during systole. Malfunction of any of these parts can lead to incompetence.

There are two different clinical syndromes of mitral regurgitation depending on whether the regurgitation develops suddenly or slowly. With chronic mitral regurgitation, usually rheumatic, the development of this regurgitation is gradual. The left atrium slowly enlarges, becomes very compliant and, even though the regurgitant volume is large, the left atrial pressure rises little, pulmonary hypertension does not develop and patients become limited eventually by low cardiac output manifest as fatigue. Atrial fibrillation is common. Physical signs include the typical pansystolic apical murmur, a prominent and hyperdynamic left ventricular impulse, a third heart sound and, if the mitral regurgitation is severe, a diastolic flow murmur at the apex and a prominent left parasternal heave.

In contrast, acute mitral regurgitation, as may occur with ruptured chordae tendinae, the regurgitation begins abruptly, the left atrium is normal size, the left atrial pressure is very high, there is marked dyspnea and prominent pulmonary hypertension.[10] Sinus rhythm is usual, rather than atrial fibrillation, and the increased force of left atrial contraction produces an easily audible fourth heart sound (Figure 3).

In contrast to mitral stenosis which is almost always rheumatic, mitral regurgitation can be the result of several causes.

Rheumatic Heart Disease

Rheumatic heart disease is the most common cause of mitral regurgitation. The valve leaflets are thickened, retracted, often calcified and held in an open position. The left atrium is often very large and, in contrast to mitral stenosis, the left ventricle becomes hypertrophied from the recurrent volume load.

Symptoms

The dominent symptom of mitral regurgitation is fatigue from low cardiac output, usually late in the course of the disease and associated with the appearance of atrial fibrillation. Contrary to previous understanding, systemic embolism is as common with mitral regurgitation as with mitral stenosis.[2,3]

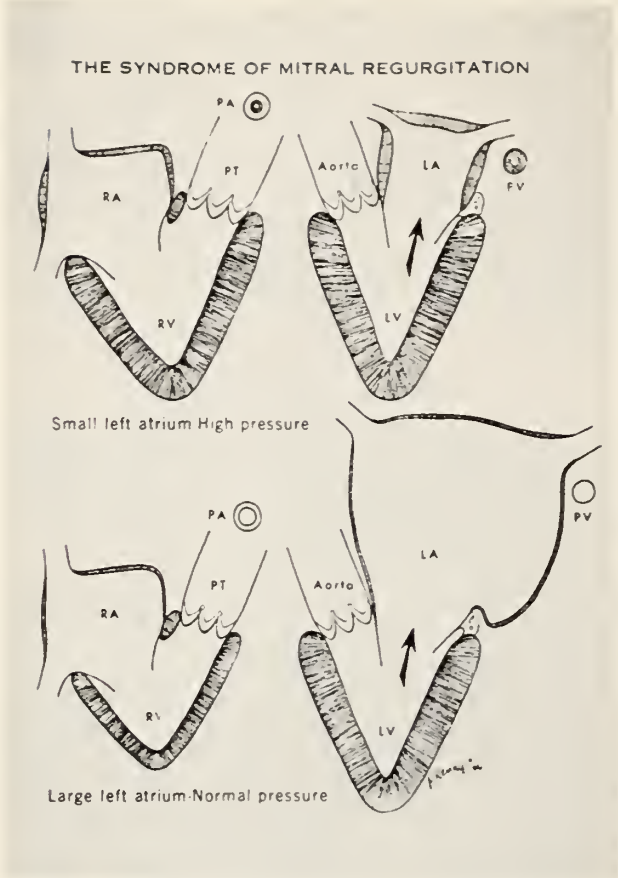


Fig. 3. The syndromes of mitral regurgitation. As indicated in the upper drawings, acute mitral regurgitation is associated with normal size left atrium and increased pulmonary vascular resistance when compared to chronic mitral regurgitation depicted in the lower drawings. From Roberts, W.C., Ann. Int. Med. 77: 1972; by permission of the author and editor. RA = right atrium, RV = right ventricle, PT = pulmonary trunk, PA = pulmonary artery, PV = pulmonary vein, LA = left atrium, LV = left ventricle.

Physical Signs

The murmur of mitral regurgitation is high pitched, usually pansystolic and heard easiest at the apex, though it may radiate widely over the precordium. It is difficult to estimate the degree of mitral regurgitation from the intensity or duration of the murmur. If the volume of regurgitation is large, there may be a third heart sound and a diastolic flow murmur at the apex. With very large regurgitant volumes, the expansion of the posteriorly placed left atrium displaces the entire heart forward in systole and can be felt as a prominent heave along the left sternal edge. The left ventricular impulse is usually prominent and hyperdynamic and the prominence of the left ventricular impulse correlates with the degree of mitral regurgitation.

The electrocardiogram and chest x-ray may show evidence of calcium within the mitral valve. The echocardiographic features of mitral regurgitation are not characteristic, but provide circumstantial evidence such as left atrial enlargement, enlargement of the hyperdynamic left ventricle and perhaps calcium within the mitral valve.

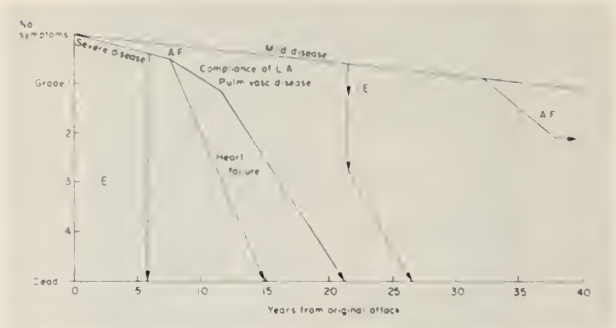


Fig. 4. The natural history of rheumatic mitral regurgitation. LA = atrial atrium, IE = infective endocarditis, AF = atrial fibrillation. From Goodwin, J.F. (1969), *Medical and Surgical Cardiology*, p. 847, Blackwell Scientific Publication; by permission of the author and publisher.

Natural History

Most patients with mitral regurgitation have only mild disability if not complicated by infective endocarditis or aortic valve disease. In some, the regurgitation gradually progresses until symptoms begin, usually with the onset of left ventricular failure (Figure 4).

Management

Mitral valve replacement is recommended for patients with disabling symptoms. It is important to emphasize that sometimes patients have disabling symptoms related to suboptimal medical management. For example, the patient with atrial fibrillation and a rapid ventricular response may be considerably improved by slowing the ventricular response with digitalis or propranolol and surgery can be postponed.

Patients with rheumatic mitral regurgitation should be given prophylaxis for recurrent rheumatic fever and infective endocarditis.[8,9] Antiarrhythmic agents may be required for control of atrial fibrillation and digitalis and diuretics may be required if pulmonary venous congestion or peripheral edema develop.

Some patients who are not suitable for surgery because of concomitant illness or age may be difficult management problems. For these patients, afterload reduction may provide marked symptomatic relief. In 1922, Wiggers showed that decreasing the arterial blood pressure decreased the severity of mitral regurgitation.[11] It is now well documented that reducing the afterload, or peripheral resistance, with vasodilator drugs can produce hemodynamic improvement in patients with severe mitral regurgitation.[12] Nitroprusside has been used for afterload reduction, and is most helpful in patients with acute mitral regurgitation, but other drugs such as nitroglycerin, isosorbide, prazocin and hydralazine have been used.

Papillary Muscle Dysfunction

Mitral regurgitation can be the result of papillary muscle dysfunction. Papillary muscle rupture, usual-

ly the result of myocardial infarction, can cause acute mitral regurgitation and the extent of the symptoms depends on the extent of papillary muscle damage. Papillary muscle rupture occurring during the course of myocardial infarction often produces severe pulmonary edema which can be fatal unless surgically corrected.

The papillary muscle may function abnormally, however, without loss of continuity or rupture and this is often related to myocardial ischemia. As the left ventricle contracts, the papillary muscle must contract at exactly the same rate to take up the slack of the chordae tendinae and hold the mitral valve closed against the increasing left ventricular pressure. The papillary muscle, an endocardial structure, has a very tenuous blood supply and is made easily ischemic, especially in the presence of coronary artery disease or left ventricular hypertrophy. This ischemia can result in papillary muscle dysfunction and mitral regurgitation. The syndrome of papillary muscle dysfunction is therefore a spectrum and may produce marked mitral regurgitation and a pansystolic murmur if the ischemia is marked, or mild mitral regurgitation with a late systolic murmur if the ischemia is mild. At times, mitral regurgitation due to papillary muscle dyscuntion may occur during spontaneous episodes of angina pectoris or, transiently, after a treadmill exercise test and the presence of this should be sought.

Papillary muscle dysfunction may be associated with cardiomyopathy. The left ventricular dilatation which accompanies forms of congestive cardiomyopathy displaces the papillary muscles laterally. As a result, contraction of the papillary muscles is exerted laterally rather than vertically and tends to keep the leaflets apart in systole with resultant mitral regurgitation. The exact mechanism for the mitral regurgitation which accompanies hypertrophic cardiomyopathy is not known. It has been proposed that, because of the hypertrophic ventricular septum, the anterior mitral valve leaflet is pulled across the left ventricular outflow tract as systole progresses causing both outflow tract obstruction and mitral regurgitation.[13] This abnormal motion of the anterior mitral valve leaflet so called "systolic anterior motion"—is easily demonstrable by echocardiography.

Chordae Tendinae

Mitral regurgitation may be the result of rupture of chordae tendinae. This usually occurs in older patients and is thought to be the result of aging, but may occur during the course of infective endocarditis. The clinical picture is similar to that of ruptured papillary muscle with the sudden onset of severe mitral regurgitation. Sinus rhythm is usually present, the left atrial size is usually normal and a loud fourth heart sound is usually heard.

Mitral regurgitation may be the result of deformed chordae tendinae or, in effect, chordae that are *too long* for the left ventricle. This is thought to be one of the mechanisms for the mitral regurgitation in patients with the systolic murmur-systolic click syndrome. In some of these patients, the valve leaflet tissue is redundant also. In this condition, as systole begins, the mitral valve is competent. As the left ventricle shortens during systole, the papillary muscle contracts normally, but can not take up all of the slack chordae and a portion of one or both mitral valve leaflets prolapse into the left atrium. When this prolapse is abruptly checked by the taunt chordae, a loud and usually single click is produced followed closely by a systolic murmur. The amount of mitral valve prolapse, and thus the amount of mitral regurgitation, varies considerably from patient to patient depending on the "length" of the redundant chordae. Some patients have prominent midsystolic clicks without any significant mitral regurgitation and others have clicks with prominent mitral regurgitation. In addition to the variation from patient to patient the amount of regurgitation, and thus the physical findings, may vary from time to time within the same patient. With maneuvers which make the left ventricle smaller, such as standing or sitting or the administration of nitroglycerin, the prolapse, and thus the click and the murmur, appear earlier in systole. In some patients only the midsystolic click is heard when examination is performed in the supine position. The venous pooling which results from standing decreases the left ventricular volume and size allowing more mitral valve prolapse with the appearance of mitral regurgitation and the typical murmur.

It is difficult to estimate the incidence and prevalence of this syndrome accurately. But these findings are frequently encountered, especially in young women, in routine cardiology examinations.[14] Most patients with these physical findings are asymptomatic though others complain of "atypical" chest pain, dyspnea, dizziness, fatigue and palpitations. An extensive evaluation of a large number of these patients has not revealed any cardiac cause for these symptoms except perhaps for the palpitations which may be related to transient supraventricular, and occasionally ventricular, rhythm disturbances.

Electrocardiographic abnormalities are frequent in patients with mitral valve prolapse, the prevalence vary depending on the selection of cases. Perhaps the most widely recognized pattern is inversion or partial inversion of the T waves in Leads II, III and AVF resembling changes seen with inferior wall myocardial ischemia (Figure 5). A wide variety of rhythm disturbances has been documented, paroxysmal supraventricular tachycardia and ventricular ectopic beats being the most frequent.

Echocardiography is often helpful in confirming the presence of mitral valve prolapse. The valve leaflets close normally, but as systole progresses, portions of one or both leaflets prolapse into the left atrium producing an abrupt posterior movement of the valve leaflet on the echocardiogram. In some patients with clinical evidence of mitral valve prolapse,

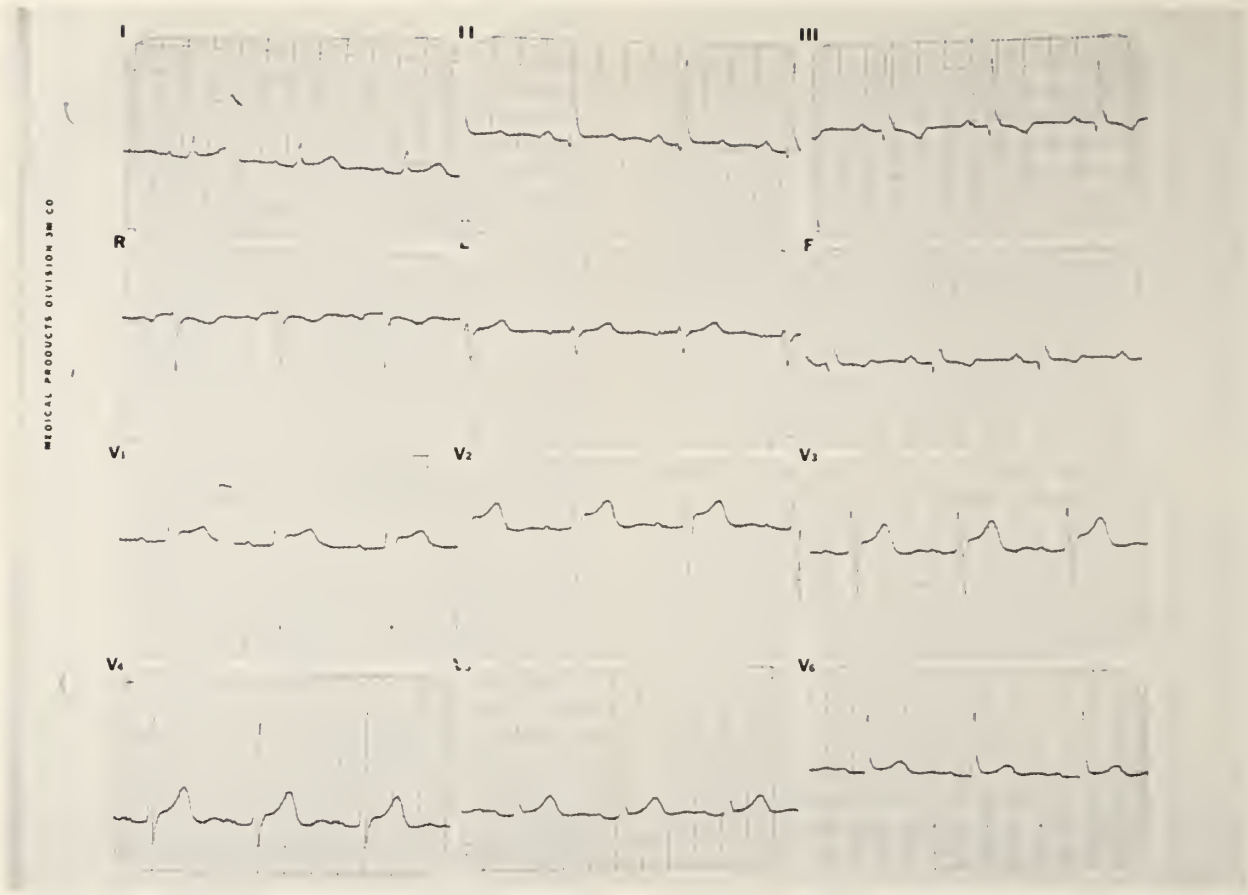


Fig. 5. Electrocardiogram from patient with mitral valve prolapse. Note the T-wave inversion in Leads III,AVF similar to that seen with inferior wall myocardial ischemia.

it is impossible to demonstrate prolapse on the echocardiogram. A negative echocardiogram, therefore, does not rule out mitral valve prolapse but echocardiographic documentation of mitral valve prolapse can provide important diagnostic confirmation.

Most patients with mitral valve prolapse appear to have little if any, reduction in life expectancy. Although uncommon, complications do occur. Ventricular ectopic beats are frequent and occasionally multifocal. Higher grades of ventricular irritability including ventricular tachycardia occur, but are less common. A few instances of sudden death have been reported in patients with mitral valve prolapse syndrome and this is presumed to be due to primary ventricular fibrillation. Supraventricular arrhythmias including paroxysmal atrial tachycardia and atrial fibrillation are frequent. Infective endocarditis has been reported in a few patients with mitral valve prolapse. Most of the patients have had a murmur of mitral regurgitation, but endocarditis has also occurred, though much less commonly, in patients with only a midsystolic click.[15] Progression to severe mitral regurgitation over a period of years may occur and this has been well documented, but in only a small number of patients. Spontaneous rupture of one or some of the redundant chordae has been described.

Management

Most patients with mitral valve prolapse have no limitations, lead normal active lives and require no treatment. Most, however, will require reassurance that the physical signs and laboratory findings which have attracted so much attention are related to an abnormality, or rather variation, in one of their heart valves that is not likely to produce any limitations or shorten their lives. Propranolol has been particularly helpful in treating the symptomatic rhythm disturbances and seems to be effective for supraventricular as well as ventricular arrhythmias. Propranolol has been used to treat the chest pain, often with good effect. Occasionally in patients with chest pain, coronary arteriography is required to exclude concomitant coronary artery disease.

Prophylaxis for infective endocarditis should be used before dental procedures and other surgery, especially in patients with murmurs. Mitral valve replacement has been performed in patients with severe mitral regurgitation which could not be controlled medically. Systemic embolism is infrequent, perhaps because the mitral regurgitation is usually mild, and anticoagulants are not usually recommended.

Left Atrial Myxoma

Tumors arising in the left atrium may grow large

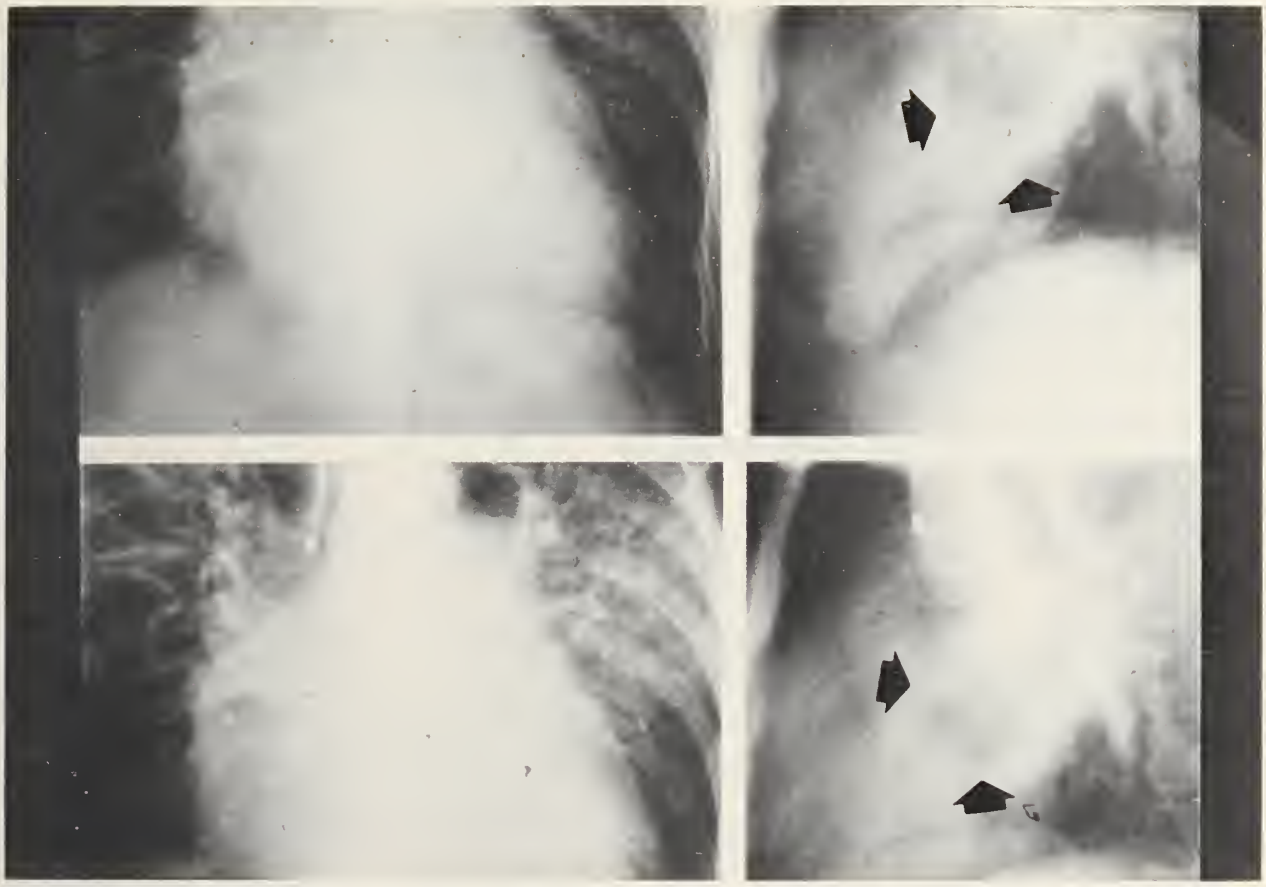


Fig. 6. Systolic (top panels) and diastolic (bottom panels) frames from cineangiogram showing large atrial myxoma (↑) best seen on lateral views.

enough to obstruct the mitral valve orifice and mimic the symptoms and findings of mitral valve stenosis. The typical tumor of this type is an atrial myxoma, a soft pedunculated tumor rising from the atrial septum in the region of the fossa ovalis. It is a fragile, soft, jelly-like tumor which is easily fragmented into large particles which embolize the systemic circulation. It may enlarge and partially protrude through the mitral valve in diastole, partially obstructing it.

Occasionally systemic embolization is the first symptom of atrial myxoma and when emblectomy is performed, the characteristic myxomatous tissue may be found on histological examination. If the tumor obstructs the mitral valve orifice, dyspnea, as in ordinary mitral stenosis appears. Constitutional symptoms are frequent and include weight loss, anemia, increased sedimentation rate, clubbing of the fingers and raised serum gama globulin, findings which, in a patient with a heart murmur, might suggest infective endocarditis.

The physical signs are similar to those produced by mitral stenosis. The murmur is usually diastolic, low pitched and heard best at the apex in the left lateral decubitus position. This is often accompanied by a loud diastolic sound, the so-called "tumor plop," that is thought to be produced when the pedunculated tumor moves from the left atrium into the mitral valve orifice. Systolic apical murmurs, due to mitral regurgitation, have been reported.[16] Sinus rhythm is usually present, a finding which would be unusual in a patient with mitral stenosis severe enough to produce similar symptoms and physical findings.

The x-ray and EKG features when present are similar to those in mitral stenosis, but there may be no abnormal findings. The echocardiogram is frequently diagnostic. The movements of the anterior mitral valve leaflet are similar to those seen in patients with mitral stenosis. In addition, however, dense echos reflected from the tumor mass within the left atrium are seen behind the anterior mitral valve leaflet.

If an atrial myxoma is strongly suspected, angiography should be performed urgently with injection of the contrast into the pulmonary artery. As this contrast material passes through the pulmonary circulation and into the left atrium, the lobulated and frequently mobile tumor is outlined (Figure 6). Once the diagnosis of left atrial myxoma is established surgery should be performed without delay.[17]

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The Incidence and Prevalence of Coronary Heart Disease in Maine

Continued from Page 302

are disabled by it. Properly conceived and administered these plans would encourage high quality medical care for the largest possible number of patients with coronary heart disease without interfering with other essential services.

Acknowledgement

I wish to acknowledge the assistance of Johanna Hunt in the preparation of this paper.

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Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The Maine Medical Association's House of Delegates, at its June 1976 meeting, adopted a regulation stating that a *minimum of 150* hours of continuing medical education is required in order to maintain membership. The policy took effect on January 1, 1977 and all members must be certified by January 1, 1980. Eligibility for certification begins January 1, 1977.

Credits required for the three-year period are as follows:

Category 1 — CME Activities with Accredited Sponsorship **(60 hours required)**	**No limit**
Category 2 — CME Activities with Non-accredited Sponsorship	**45 hours**
Category 3 — Medical Teaching	**45 hours**
Category 4 — Papers, Publications, Book and Exhibits	**40 hours**
Category 5 — Non-supervised individual CME Activities	**45 hours**
Category 6 — Other Meritorious Learning Experience	**45 hours**

Only active, dues-paying members are required to report. Please fill in your activity report promptly and return to the M.M.A. office, P. O. Box 250, Brunswick, Maine 04011.

New MMA Headquarters in Augusta Opens This Month - - -

Effective the week of August 20 the Association will do business from its new headquarters at 524 Western Avenue, Augusta. Committee members attending meetings at the new headquarters should look for the circular drive just west of Trends Furniture store on Route 202, west of the turnpike interchange in Augusta. The building itself is a split-level home with light grey siding and a red brick lower level.

Operations at the new location will begin without all the required services. However, phone service will be available and members will be notified of the new number as soon as it is a certainty. Mail should continue to come to Box 250, Brunswick, Maine until further notice. It will be transported to the Augusta office by a member of the office staff who commutes from Brunswick until we are able to work out the best delivery option available in Augusta.

CME Credits Mailed - - -

Seventy-five physicians who completed evaluation forms of the scientific sessions at the 1979 Annual Session of the Association have been mailed certificates attesting to the credits earned. The completed evaluation sheets also give the Association some guidance in the organization of future programs.

Attorney General Announces Medicaid Fraud Control Unit - - -

Excerpts from a July 13 letter from Guy P. Seaberg, Assistant Attorney General and Chief, Medicaid Fraud Control Unit:

On June 25, 1979, the Medicaid Fraud Control Unit (MFCU), a division of the Office of the Attorney General, formally commenced operation. It is the responsibility of the Unit to detect, investigate and prosecute - criminally and civilly - intentional fraud by providers of goods and services who are reimbursed under the Maine Medicaid Program.

Among the Unit's responsibilities will be the prosecution of cases involving: fraud in the administration of the program; embezzlement of patients' funds by institutional providers; physical abuse of patients; intentional overutilization for the principal purpose of generating excessive Medicaid payments; and false statements in annual cost reports submitted to the Department of Human Services.

It is imperative that the MFCU enlist the aid and cooperation of professional associations and organizations like your own in bringing instances of potential fraud to our attention. Only in this manner can we effectively reduce those incidents of fraudulent conduct which adversely affect the efficient operation of the vast majority of honest and competent providers, and tarnish the image of publicly financed and administered health care programs.

It should be immediately apparent that meaningful efforts by your organization to identify and eliminate fraud would be welcomed by the majority of your members and the public alike. As you may already be aware, the MFCU is a serious and concerted effort

by the Office of the Attorney General to attend to the problems of fraud and abuse; accordingly, you may be assured that the office will be responsive to your efforts.

Your anticipated cooperation is appreciated.

Five Maine Hospitals To Receive AMA Sponsored CME Programming Via Satellite - - -

On August 28 and 29, 1979, the American Medical Association will transmit a total of four hours of continuing medical education to several hundred U.S. hospitals via communications satellite.

Time for the broadcasts has been made available by the American Hospital Association, which will be transmitting daily programming in conjunction with its Annual Meeting.

The AMA-sponsored programs are "Risk Management" on Tuesday, August 28 and "Inflammatory Bowel Disease" on Wednesday, August 29. Both programs will be transmitted starting at 2:00 P.M. EST.

These programs will be interactive in that physician viewers at each hospital receiving site will be able to ask questions of the faculty in the Chicago studio by toll-free telephone and will see and hear the answer.

Augusta General Hospital, Central Maine Medical Center, St. Mary's General Hospital, Mid-Maine Medical Center and the Veterans Administration Center at Togus are scheduled to receive the broadcasts.

AMA Warns Of Efforts To Regulate Physician Supply - - -

Efforts to regulate physician supply are underway in several states and similar proposals are likely to develop in other states, the AMA warned in a memorandum to constituent associations and specialty societies. In Hawaii and Rhode Island, state health planning agencies, are seeking to impose certificate-of-need licensure based on predetermined estimates of the number of physicians required. In California and New York, health planners are working to limit the number of physicians by regulating residency training.

California Medical Association Discontinues Relative Value Studies -

As a result of a complaint filed by the Federal Trade Commission the CMA has signed a consent order which requires, among other things that the CMA:

(a) Stop publishing and participating in the development of relative value studies;
(b) Withdraw the relative value studies it has already published;
(c) Stop suggesting and instructing that conversion factors may be computed and applied to units contained in relative value studies;
(d) Distribute a copy of the complaint and consent order to CMA relative value study recipients; and
(e) Notify recipients of CMA's relative value studies to return them to CMA.

The FTC complaint alleged that CMA's relative value studies have the effect of influencing fees charged by physicians. The consent agreement with the FTC states that it is for settlement purposes only and does not constitute an admission by the CMA of the charges in the complaint or that the law has been violated.

In accordance with the provisions of the FTC's order, you are to cease using and to return all copies of any CMA relative value study in your possession.

Car Rental Discounts For MMA Members - - -

AVIS has a series of discounts available to members of the Maine Medical Association.

You will receive 25% off regular time and mileage rates in the continental United States. There are no discounts available on AVIS Special Supersaver Rates.

For world travelers there is also a discount from AVIS' regular foreign rates.



The attached card should be removed and placed in your wallet. Simply present your discount card when renting a car. The I.D. number on the card will trigger your discount on the AVIS computer. This card must be used for you to receive your discount.

Remind Your Estate Planner - - -

Physicians in their estate planning should make note of their pay into and possible pay out by the J.U.A. Stabilization Reserve Fund to provide their executors with info needed to follow up when disbursements are eventually made. It does not appear likely that disbursements will be made for at least 10 years and possibly as long as 18 years. In the meantime the Fund is receiving interest from government securities reported to be in the range of 7½% to 8%.

Medi Maine Suit Concluded - Favorably - - -

In 1976 the State of Maine attempted to regulate the purchase by private physicians of diagnostic equipment. A group of private physicians had purchased a CAT scanner and was performing diagnostic procedures. The State Department of Human Services decided that it was not favorable to private ownership of this type of equipment but the Department was aware that private physicians were not required to obtain its approval prior to purchase of capital equipment. Thus, the Department decided to try to regulate this aspect of the private physicians' practice by refusing to reimburse the physicians for that portion of the Medicaid fee which the State attributed to the cost of purchasing and maintaining the capital equipment.

Although there was no legal precedent for this action, the State decided that it had the inherent power to regulate the purchase and use of capital equipment by use of the Medicaid fee mechanism - a blatant attempt to regulate physicians' practices in an area previously left to the physicians' discretion. The Department's decision had broad implications because the State could have extended this principle to cover purchase of any capital equipment including x-ray, lasers, computer systems, or even the construction of medical facilities or offices by private physicians.

The owners of the CAT Scan equipment, Medi Maine Health Associates, brought suit against the State of Maine alleging that the new regulations were void and illegal. The Maine Medical Association joined the suit on behalf of all doctors in the State.

The Court in a judgement and decree filed and entered on July 2, 1979 found that the regulation at issue was in fact void and unenforceable because it failed to reimburse the physician for the cost of using his privately purchased equipment. In essence, the Court told the State that it had no business regulating the purchase of equipment by private physicians by means of the fee

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mechanism. The Court went on to require that future fees for this type of equipment must be fair and equitable and must include payment for the physician's services *and* for the use of his equipment.

The decision is a significant victory for the Association in terms of establishing specific rights for private physicians who participate in the Medicaid program. The three year battle against a tax-dollar supported opposition was expensive for the Association and even more so for Medi Maine Health Associates.

Attorney General's Office Feels Second Opinion Activity May Violate Maine Antitrust Laws - - -

Assistant Attorney General Stephen L. Wessler of the Consumer and Anti-trust Division on May 29 requested minutes of the November 18, 1978 meeting of the Androscoggin County Medical Society indicating that he was "---concerned that the adoption of a motion opposing the rendering of free second opinions violated the Maine antitrust laws, 5 M.R.S.A. §207 and 10 M.R.S.A. §1101."

Four weeks later on June 27, Mr. Wessler wrote MMA legal counsel saying:

"In order to fully evaluate the activities of the various chapters of the Maine Medical Association regarding second opinions, I need to learn more details concerning the recent action of the Cumberland County Medical Society. I would appreciate it if you would send me a copy of any policy statements adopted by the Cumberland Society as well as the minutes of the meeting during which the policy was adopted. After reviewing these materials, I will be back in touch with you."

Two observations:

1. This type of pressure does not enhance free debate concerning new medical programs that may extend substantial benefits to Maine citizens. Other county societies may now think long and hard before even discussing the many types of second opinion programs. It could result in a loss of medical initiative and ability to discuss freely changes which enhance medical progress.
2. It's expensive to defend yourself against government lawyers.

Excerpts From

Historical Sketch of Maine Medical Association (1st 50 Years) - - -

by Charles O. Hunt, M.D., Portland

The Maine Medical Association in the 1800's was the moving force which persuaded the Legislature of the State of Maine to establish:

1. A charter, funds and land to construct the Maine General Hospital in Portland (1870)
2. A State Board of Health (1885)
3. A Board of Licensure and Registration in Medicine (1888)
4. A grant of one half a township to construct a "new building" for the Medical School of Maine at Brunswick (1860)

Success in those days was not 100%—The Legislature repeatedly refused to pass a complusory vaccination (smallpox) law which the Maine Medical Association had proposed.

Transcatheter Embolization of a Posttraumatic Renal Pseudoaneurysm

Douglas F. Cowan, M.D.*

Introduction

Immediate or delayed posttraumatic hemorrhage is a well recognized complication of tissue damage requiring rapid diagnosis and treatment. The utility of angiography to define the cause and precise location of significant hemorrhage is clearly established. Likewise, transcatheter therapeutic embolization of bleeding sites to obviate surgical intervention is well documented.[1-8] Pseudoaneurysms of traumatized arteries are a surprisingly common sequela of vascular trauma. They may occur immediately following injury or develop later as a consequence of delayed breakdown of traumatized vascular walls.[9-11] Whether they occur early or late, once diagnosed, pseudoaneurysms pose a difficult dilemma for the physician managing the patient. The potential for rupture as a result of increasing size and/or further breakdown of the vessel wall is clearly documented.[10] This necessitates close clinical monitoring or surgical intervention to prevent possible life-threatening hemorrhage.

This report details the diagnosis and subsequent transcatheter embolization of a pseudoaneurysm of the kidney in a patient who presented with the delayed onset of hematuria following apparently benign trauma to the left flank several months earlier.

Case Report

A 35-year-old male was admitted with gross hematuria three months following a stab wound to the left flank. At the time of initial injury, there was no hematuria or evidence of trauma to the left kidney. An IVP at that time was normal except for a small nonobstructing right ureterocele. The hematocrit remained stable for 48 hours and the patient was discharged. Two days prior to his admission for hematuria, he was helping to lift a car out of a ditch, experienced left flank pain, and subsequently developed gross hematuria. An IVP at an outside hospital was interpreted as normal, except for the small right ureterocele which was unchanged. The patient was transferred to our institution for diagnostic arteriography. The angiogram demonstrated a 4 x 2 cm. pseudoaneurysm of the left kidney arising from a lower pole branch renal artery (Fig. 1). Gelfoam embolization with four small emboli resulted in total occlusion of the neck of the pseudoaneurysm (Fig. 2a). Permanent obliteration was demonstrated at the time of followup angiography three months later (Fig. 2b). The patient has remained normotensive with no recurrence of hematuria.

Discussion

The mechanisms of posttraumatic pseudoaneurysm formation are not entirely clear. Unlike true aneurysms that are lined with vascular endothelium and surrounded by intima and media, pseudoaneurysms are lined by organized fibrous tissue as a result of disruption of the vessel wall. Following trauma, arteries may be completely transected with retraction of the proximal and distal ends away from the site of fracture, or only a portion of the vessel wall may be torn. Free hemorrhage often results, but not necessarily so. If there is an incomplete tear of the vessel wall or a complete tear with continuity of the surrounding perivascular tissue, the blood will be contained at the site of injury. A focal bulge (pseudoaneurysm) may occur as the arterial pressure stretches the surrounding tissues until the arterial blood pressure is balanced by the inward pressure of the remaining vascular wall and surrounding tissues. Obviously, the distal end of the traumatized vessel must be open and in close enough proximity so that blood flow through the traumatized vessel persists.

Once a pseudoaneurysm forms, if there is further breakdown of the false wall or if intraarterial pressure increases, the diameter of the pseudoaneurysm will increase as the false wall is stretched. By LaPlace's law, further increases in diameter should require smaller and smaller pressure increments as long as the walls of the pseudoaneurysm remain elastic. Ultimately free rupture may result.

Arteriography immediately following vessel trauma may have several different appearances. (1) The proximal vessel may be totally occluded due to intense spasm of the proximal end. (2) There may be free extravasation of contrast material from the traumatized vessel if spasm is insufficient to obliterate the lumen and the vessel wall plus surrounding tissue are disrupted. (3) A focal bulge or saccular outpouching from the vessel wall will be opacified with contrast material if a traumatic pseudoaneurysm results.

Typically, an initial arteriogram for acute traumatic hemorrhage will demonstrate extravasation from large arteries. A repeat examination, however, necessitated by delayed hemorrhage will often reveal additional free extravasation as well as the appearance of one or more pseudoaneurysms. As the initial obstruction secondary to vascular spasm at the site or sites of vessel injury subsides, frank hemorrhage or pseudoaneurysms are likely to follow.

In our patient, the initial stab wound caused no hematuria or other evidence of bleeding. The knife did traumatize the left kidney, however, and a large pseudoaneurysm resulted. Subsequently, with intense straining it is postulated that there was a small rupture of the pseudoaneurysm, most likely due to transient increase in intraarterial pressure. Although the bleeding subsided spontaneously, there was no way to predict whether bleeding would recur and, therefore, it was elected to embolize the pseudoaneurysm prophylactically to prevent a further episode.

*From the Eastern Maine Medical Center, Bangor, Maine 04401.



Fig. 1a



Fig. 1b



Fig. 1c

Fig. 1 a) Late main stream abdominal aortogram demonstrating a 2 x 4 cm. lobulated pseudoaneurysm at the lower pole of the left kidney. b) Selective left renal artery injection confirming the origin of this pseudoaneurysm from a left lower pole renal artery (arrow). c) Subselective catheterization of the lower pole branch renal artery supplying the pseudoaneurysm and a small amount of adjacent normal renal parenchyma. Note the spasm of the lower pole branch compared to b.

The advantages of transcatheter embolization for posttraumatic hemorrhage are obvious. The procedure is performed under local anesthesia so that surgery with its associated increased morbidity can be avoided. Once angiography has determined the bleeding site, transcatheter embolization of the feeding artery can proceed immediately, usually with minimal tissue damage. Surgical removal of the renal pseudoaneurysm in this case almost certainly would have necessitated heminephrectomy.

Therapeutic embolization of the renal bed is ideal since there is a single vascular supply and few intrarenal collateral vessels.[12-16] Subselective arterial catheterization is technically easy in most instances and the rapid renal arterial blood flow makes reflux of Gelfoam emboli retrograde into the aorta unlikely.

Renovascular hypertension is a theoretical complication of transcatheter embolization of the kidney, but clinically it is rarely a complication.[12,14,16] Infarction of renal tissue does not activate the renin-angiotensin system and there is apparently insufficient viable ischemic tissue stimulated to secrete renin.[13,17]

Not all pseudoaneurysms are readily treated with embolization. In the extremities where there are numerous native collateral vessels, embolization of bleeding pseudoaneurysms may be ineffective due to collateral supply.[9] In theory, the same may be true



Fig. 2a



Fig. 2b

Fig. 2 a) Contrast injection immediately following transcatheter Gelfoam embolization with the catheter tip more proximal than in Fig. 1c. There is total occlusion of the vessel supplying the pseudoaneurysm. Two additional small emboli are seen in peripheral renal branches of an adjacent lower pole renal artery (arrows). b) Selective left renal artery injection 3 months following embolization documenting permanent obliteration of the pseudoaneurysm. There is cortical indentation at the site of pseudoaneurysm secondary to localized infarction of renal tissue with incomplete nephrogram at the lower pole secondary to small Gelfoam emboli to peripheral lower pole branches. The lack of opacification of the medial upper pole is due to its independent supply from an additional artery arising directly from the aorta.

for pseudoaneurysms of the pancreaticoduodenal arcade due to extensive collateral communications. Regardless, transcatheter embolization is often effective even with collateral vessels since intra-arterial pressure at the site of extravasation may be sufficiently reduced so that the patient's intrinsic clotting parameters cause cessation of hemorrhage. In the special case of pseudoaneurysms that occur following pancreatitis with enzyme digestion of the vessel wall, embolization may exacerbate bleeding due to the extremely delicate walls of these pseudoaneurysms.[10] They have been reported to rupture during subselective angiography or embolization if the catheter tip partially or completely occludes the supplying vessel. The pressure within the pseudoaneurysm may rise abruptly when contrast material or emboli are injected. For this reason, our catheter was withdrawn more proximal in the renal artery when the Gelfoam emboli were injected.

Several technical points should be stressed. The catheter tip should be as peripheral as possible without vessel occlusion to minimize damage to normal surrounding tissue. Small emboli should be injected first to occlude the offending vessel as peripheral as possible to minimize collateral supply distal to the embolus. If small emboli are ineffective, larger emboli can then be employed. Once embolization has decreased flow to the desired area, additional emboli must be introduced with extreme caution since antegrade flow is reduced and reflux of emboli back into the aorta is much more likely. Often only a small number of emboli are required to occlude the orifice of the pseudoaneurysm. If flow to the pseudoaneurysm is high relative to normal tissue, then emboli will preferentially travel toward it. This is particularly true with active bleeding where arteriolar pressure at the bleeding site may be quite low with resultant rapid flow to the site of extravasation.

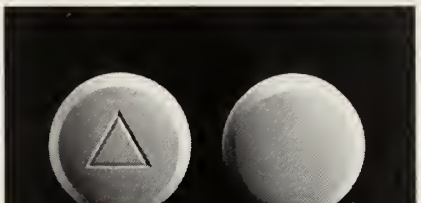
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The Maker

Examining a Few Myths About Prescribing.



Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand-name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to a reference product. As y know, there is substan literature on this subje affecting many drugs, cluding such antibioti as tetracycline and ery thromycin. The record drug recalls and court actions affirms strongl that there are differen among pharmaceutica companies and their products. Research-intensive companies have far better records than those that do no r search and may practi minimum quality assu ance.

MYTH: Industry favors only "expensive" brand names and denigrates a generics.

FACT: PMA companie make 90 to 95 percen the drug supply, inclu ing, therefore, most of generics. Drug nomen clature is not the impo tant point; it's the con tence of the manufac- turer and the integrity the product that coun

Matters.

MYTH: Generic options almost always exist.

FACT: About 55 percent of prescription drug expenditure is for single-source drugs. This means, of course, that for only 45 percent of such expenditure, is a generic prescribing option available.

MYTH: Generic prescriptions are filled with inexpensive generics, thus saving consumers large sums of money.

FACT: Market data show that you invariably prescribe—and pharmacists dispense—both brand and generically labeled products from known and trusted sources, in the best interest of patients. In most cases the patient receives a proven brand product. Savings from voluntary or mandated generic prescribing are grossly exaggerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

PMA

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

Percutaneous Transluminal Angioplasty

A Nonoperative Treatment of Occlusive Vascular Disease

Thomas J. Black, M.D.*

Introduction

Percutaneous transluminal angioplasty (P.T.A.), a non-operative angiographic approach to the treatment of vascular stenoses and occlusions, was first described by Dotter and Judkins in 1964.[1] Since that time a great deal of experience in its use has been gained, primarily by Dotter and his associates in this country and by a number of angiographers in Europe.[2,3,4,5,6,7,8,12] During the past couple of years, much enthusiasm has been generated in this country for the procedure and its use has become widespread. The current trend toward greater use of P.T.A. in the U.S. is attributable to: 1) favorable long term results reported by various authors; 2) recent availability of specially designed balloon dilatation catheters which have largely replaced the earlier coaxial catheter technique resulting in improved results with fewer complications; and 3) excitement stemming from successful use of the technique in treating renovascular and coronary artery occlusive disease.[9,10,11]

Since June 1978, P.T.A. has been performed at the Eastern Maine Medical Center. The first four patients are presented to illustrate use of the technique. The technical details of P.T.A. have been reported elsewhere and will not be discussed.

Case Reports

Case 1

A 79-year-old hypertensive diabetic man was admitted on 6/6/78 with rest pain and numbness of his right foot. The patient had severe ASCVD and had previously undergone the following vascular surgical procedures: successful right femoropopliteal bypass on 11/16/71 using an 8 mm dacron graft; two attempts at left femoropopliteal bypass with both attempted grafts eventually undergoing thrombosis owing to poor distal runoff; and left lumbar sympathectomy on 3/21/75. On admission, the right femoral pulse was markedly diminished. Angiography (Fig. 1a) revealed an 80-90% focal concentric stenosis of the right external iliac artery at its origin with a 51 mm Hg resting systolic gradient. The femoropopliteal graft was patent but the popliteal artery was occluded distally with the peroneal artery, reconstituted in the proximal calf, constituting the major non-collateral vessel supplying the foot. It was felt that elimination of the iliac stenosis might improve perfusion pressure of the vessels supplying the foot and thereby relieve his rest pain.

On 6/9/78, the patient underwent P.T.A. of the external iliac stenosis using a 9 French (8 mm balloon diameter) Gruntzig balloon catheter‡ which was introduced retrogradely via the right common femoral artery by means of Seldinger technique under local anesthesia. Repeat angiography (Fig. 1b) performed immediately following P.T.A. revealed significant increase in vessel caliber at the previous site of stenosis with no measurable iliac pressure gradient. The femoral pulse was normal to palpation following the procedure and the patient noted cessation of his ischemic pain. He was discharged two days later on aspirin and Persantine® therapy.

On 9/19/78, the patient was readmitted with recurrent intermittent rest pain of his right forefoot. On physical examination, his right femoral and popliteal pulses remained unchanged. Angiography (Fig. 1c) revealed wide patency of the previously dilated iliac lesion with some apparent increase in luminal caliber since the angiogram performed immediately following P.T.A. There was no iliac pressure gradient. A run-off arteriogram revealed interval development of a small aneurysm at the distal anastomosis of the right femoropopliteal graft though angiographically the peripheral vessels remained unchanged. It was felt that perhaps progression of small vessel disease or microemboli from the aneurysm might account for recurrence of symptoms. During his hospitalization, the patient's pain subsided and it was elected to forego further surgery at that time.

Case 2

A 38-year-old woman was admitted with progressive bilateral buttock, thigh and calf claudication. The patient first experienced symptoms of vascular insufficiency of similar distribution at age 28. Angiography in 1970 revealed diminutive caliber of her infrarenal aorta with involvement of her common iliac arteries. She underwent successful aortoiliac endarterectomy; pathologic material revealed cystic medial necrosis of the aorta. Postoperatively, she did well until the Fall of 1972 when ischemic symptoms gradually recurred. Angiography revealed bilateral iliac stenoses and on 1/12/73 she underwent aortoiliac endarterectomy with dacron patch angioplasty and bilateral lumbar sympathectomy. Again she did well until the Fall of 1975 when she gradually developed progressive bilateral claudication. Angiography again revealed bilateral common iliac artery stenoses and on 9/21/76 she underwent aortobilateral common iliac bypass using a dacron graft. Pathologically the resected stenotic segments were composed of fibrotic intimal plaques. The patient was once more free of symptoms until the Spring of 1977 when she again noted bilateral buttock, thigh and calf claudication with fast walking. At admission on 11/27/78, the left femoral pulse was barely palpable and the right femoral pulse was only slightly stronger. Angiography performed by translumbar approach (Fig. 2a) revealed critical stenoses at the graft-iliac artery anastomoses bilaterally. After consideration of therapeutic alternatives, it was elected to attempt P.T.A. On 12/8/78, the patient underwent transluminal angioplasties of both iliac stenoses using a 7 French (1.5 cm. long/6 mm. diameter balloon) Gruntzig balloon catheter introduced by bilateral retrograde femoral artery puncture. On the left, a pre-P.T.A. resting systolic pressure gradient of 38 mm Hg was reduced to 6 mm Hg following dilatation and a significant increase in luminal caliber was noted (Fig. 2b, 2c). On the right, no preangioplasty pressures were obtained and the gradient following P.T.A. was 6 mm Hg. Again, post procedural angiograms revealed increased vessel caliber (Fig. 2d, 2e). Following the procedure, the patient's lower extremity pulses were all normal to palpation and she was discharged the next day on aspirin and Persantine therapy. At 3 month clinical followup, she continues to do well with unchanged pulses and no recurrence of symptomatology.

Case 3

A 68-year-old hypertensive man was admitted on 1/10/79 for elective P.T.A. of a severe stenosis involving the distal anastomosis of a left saphenous vein femoropopliteal graft. The patient, a one pack per day smoker, who had suffered a CVA 8 years ago with resultant left hemiparesis, had undergone the following vascular surgical procedures: left iliofemoral bypass (8 mm dacron graft) and left femoropopliteal saphenous vein bypass on 2/78 with successful alleviation of left foot rest pain; and left-to-right femoro-femoral bypass (6 mm dacron graft) and right saphenous vein femoropopliteal bypass on 10/78 with resultant cessation of rest pain involving his right foot. Angiography (Fig.

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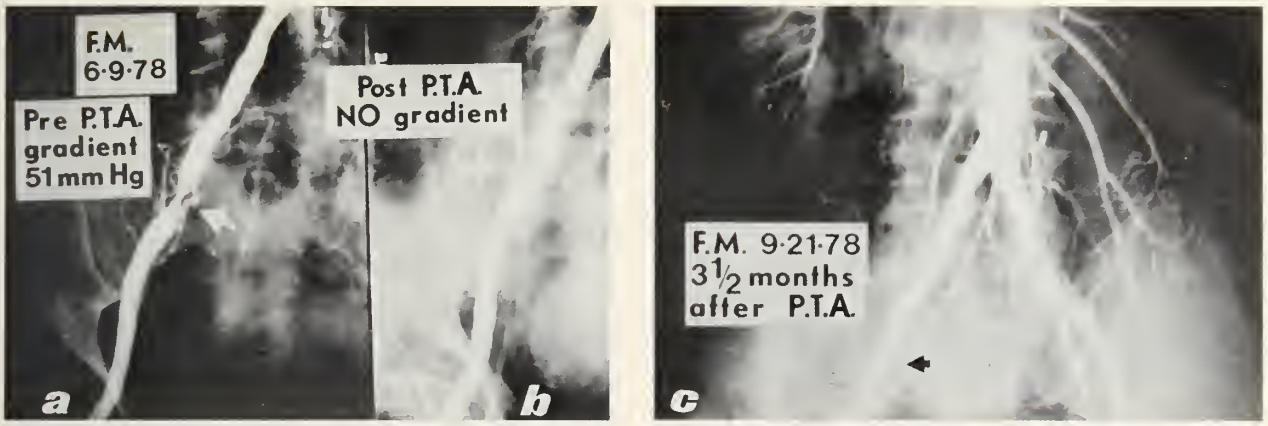


Fig. 1—Case 1. Dilatation of external iliac stenosis. Appearance of stenotic segment (arrows) before (a) and after (b) dilatation. (c), 3½ months later, continued wide patency of dilated segment.

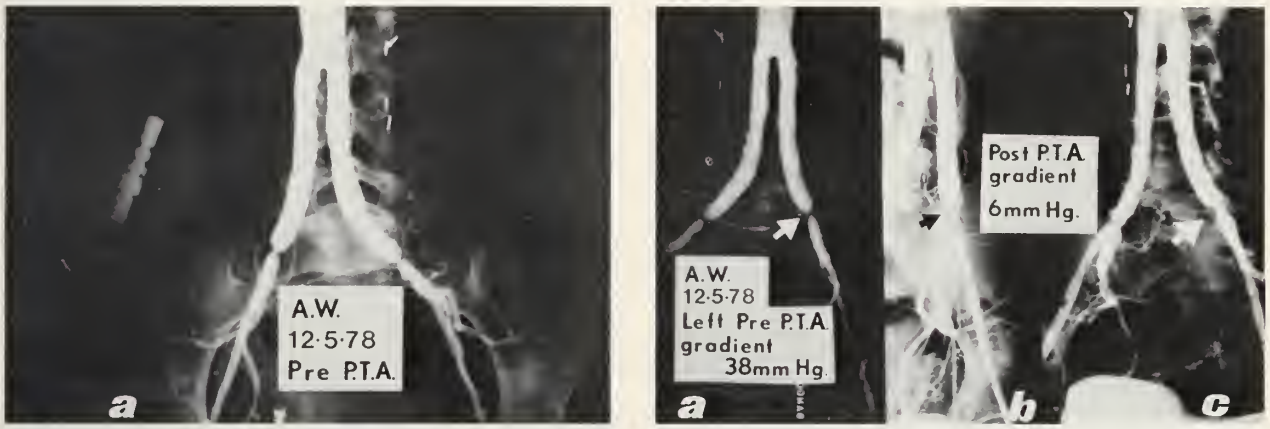
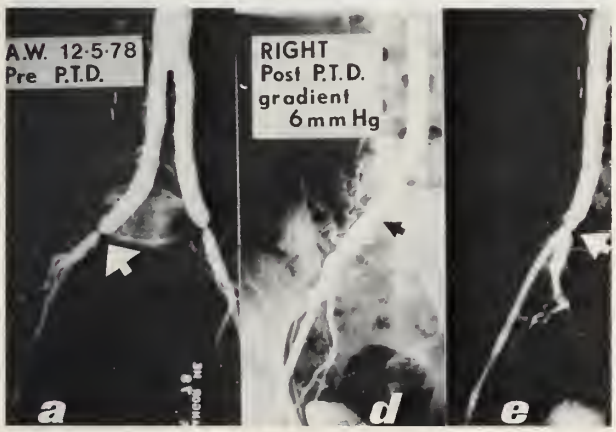


Fig. 2—Case 2. Dilatation of graft-iliac artery anastomotic stenoses (arrows). Appearance of anastomoses before (a) and after dilatations of left (b, LPO oblique; c, frontal view) and right (d, frontal view; e, RPO oblique) limbs of graft.



3a) performed prior to the 10/78 surgery revealed a critical stenosis of the distal left femoropopliteal anastomosis and vascular studies demonstrated a 40 mm Hg thigh-calf resting systolic pressure gradient. Owing to concern for possible graft thrombosis secondary to outflow obstruction, the patient was electively admitted for P.T.A. on 1/10/79. At admission there was a loud left popliteal bruit and no palpable popliteal or foot pulses. On 1/11/79, the patient underwent P.T.A. using a 7 French (2.0 cm. long/5 mm. diameter balloon) Gruntzig balloon catheter introduced in an antegrade (downstream) fashion through the left iliofemoral dacron graft under local anesthesia by means of Seldinger technique. Immediately following the P.T.A. the popliteal and dorsalis pedis pulses were normally palpable and an angiogram (Fig. 3b) revealed significant increase in luminal caliber. The patient was discharged the next day on aspirin and Persantine therapy.

Vascular studies performed immediately following angioplasty and at one month followup revealed no residual resting thigh-calf pressure gradient. The patient remains asymptomatic.

Case 4

A 39-year-old woman was admitted with progressive left calf claudication of 4 months' duration. At the time of admission she could walk only 30 feet before developing ischemic pain. Relevant history included 20 pack years of cigarette smoking. On physical examination, neither the left popliteal nor left pedal pulses were palpable. Doppler studies revealed a 40 mm. resting systolic thigh-calf gradient on the left. Angiography revealed a localized segmental occlusion of the left popliteal artery though retrograde filling of a markedly narrowed segment was provided by collaterals (Fig. 4a,b). The anterior tibial artery was occluded distally. Therapeutic options were considered and the patient elected to undergo P.T.A. On 4/24/79, the patient underwent P.T.A. of the segmental popliteal occlusion using a 7 French (2 cm. long/5 mm. diameter balloon) Gruntzig balloon catheter. Angiography immediately following the procedure (Fig. 4c,d) revealed patency of the popliteal artery at the point of previous occlusion with no significant residual vessel narrowing. The patient's popliteal and posterior tibial pulses were normal to palpation and no resting systolic thigh-calf gradient was present. The patient noted no claudication the following day upon walking distances greater than those which would have produced symptoms prior to P.T.A. and she was discharged two days following angioplasty on Coumadin® therapy.

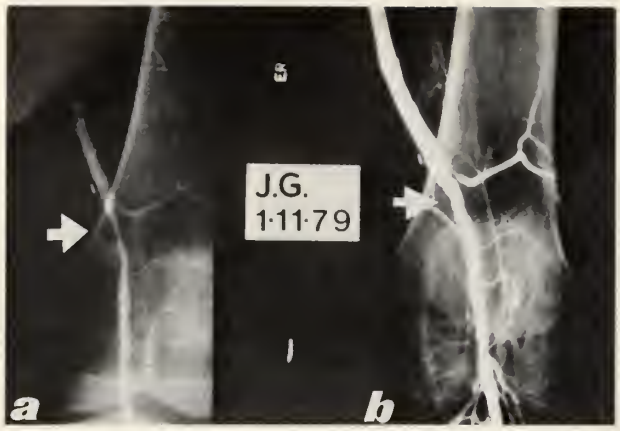


Fig. 3—Case 3. Dilatation of saphenous vein-popliteal artery anastomotic stricture. Appearance of anastomosis before (a) and after (b) dilatation.



Fig. 4—Case 4. Recanalization of short segmental popliteal artery occlusion. Appearance of popliteal segmental occlusion in frontal (a) and lateral (b) views before P.T.A. and in oblique (c) and lateral (d) views after P.T.A.

Discussion

Since its introduction in 1964, P.T.A. has been successfully employed to treat vascular stenoses of diverse etiologies and to reestablish prolonged luminal patency in cases of atherosclerotic vessel occlusion. The mechanism of luminal enlargement or of recanalization in the case of atherosclerotic lesions appears to relate to the tendency of these lesions to undergo permanent compression when acted upon by an expansile intraluminal force.[1,5,6,7] During angioplasty, this force is produced either by passing progressively larger tapered catheters across a stenotic lesion or by positioning a balloon catheter at the point of vessel narrowing and, by inflating the balloon, effecting dilatation. The fixed nature of the compression is attested to by follow-up clinical, vascular laboratory and angiographic studies which demonstrate prolonged luminal enlargement and elimination of hemodynamically significant obstructions in a large percentage of cases. The mechanism of success in cases of fibrotic lesions or of fibromuscular dysplastic lesions is as yet unknown though angioplasty has been effectively applied to treatment of post surgical anastomotic stenoses at various sites as well as to treatment of renal artery stenoses produced by fibromuscular dysplasia.[14,15] Another as yet unanswered question concerns the fate of frequently noted luminal irregularities which are apparent on angiograms performed immediately following angioplasty but which are not present on follow-up studies as noted in our first case. Presumably these irregularities, which may be composed of ruptured intima or linearly interrupted plaque, are cleared by means of fibrinolysis or through clinically insignificant peripheral embolization.

Successful application of this procedure appears to relate to methodology employed, to proper patient selection and, as recently noted, to long term anticoagulation particularly in the case of treated femoropopliteal lesions.[14] In a recent report of 300 patients treated principally by means of his balloon catheter, Gruntzig indicated the following results: primary success in dilatation of iliac stenoses in 92% of cases with demonstrated two-year patency in 87%; and primary success in 84% of treated femoropopliteal stenoses or short, segmental occlusions (≤10 cm. long) with 72% patency at two-year follow-up.[10] The long term follow-up of these patients is of course unknown, though various authors have indicated that, whereas sites of previous angioplasty may undergo occlusion with prolonged follow-up, the rate of reocclusion diminishes after the first two years following P.T.A.[14] In general, short concentric noncalcified stenoses or short, segmental femoropopliteal occlusions 10 cm. or less in length are more likely to be successfully dilated than are irregular, calcified or long segment occlusions though long term patency has been reported even for these lesions. Similarly, femoropopliteal occlusions which have been present and symptomatic for less than one year are more likely to be successfully treated than are more long standing lesions. Use of platelet inhibitors during and after P.T.A., use of intraarterial heparin during the procedure and long term anticoagulation with Coumadin have all contributed to improved primary results and to prolonged rates of patency.

The overall complication rate when using the Gruntzig balloon catheter is approximately 8.5% which includes, in addition to the usual minor complications of angiography, puncture site hemorrhage or pseudoaneurysm formation, peripheral embolization and thrombotic occlusion either at the puncture site or at the site of dilatation.[10] In 2-3% of cases surgery will be required, usually to correct one of these complications. Peripheral embolization, although a concern, occurs infrequently. Gruntzig noted angiographic evidence of peripheral embolization in 5% of his 300 treated patients but in none of these cases were these clinically apparent events.[10] That peripheral embolization occurs so infrequently probably relates in part to the fact that with the balloon catheter the dilatation force is radially applied without significant longitudinally oriented shear effect. Complications have been reduced from early reports owing to use of balloon catheters, to intraprocedural anticoagulation and to prophylactic use of intraarterial vasodilators to counteract possible vasospasm.

P.T.A. may be employed in a variety of clinical situations including the following: 1) cases of possible limb salvage prior to anticipated amputation; 2) patients for whom reconstructive surgery is likely to prove unsuccessful owing to poor run-off but for whom angioplasty, a procedure of lesser risk, offers possible relief; 3) patients who ordinarily would be considered candidates for reconstructive surgery but who either refuse surgery or for whom there are medical contraindications to surgery; 4) patients who have strictures related either to previous sites of endarterectomy or to surgical anastomoses; and 5) settings in which P.T.A. of one lesion might simplify the surgical approach to another.[13] For example, angioplasty of a critical iliac stenosis in a patient with contralateral iliac artery occlusion would enable the reconstructive surgeon to limit his procedure to femorofemoral bypass. Similarly angioplasty of an iliac stenosis prior to ipsilateral femoropopliteal bypass might lessen the risk of possible graft thrombosis.

Advantages of P.T.A. over surgery for appropriate lesions include use of local rather than general anesthesia and low risk of complications. There is a low probability of worsening the clinical picture. The procedure is repeatable in the event that delayed reocclusion occurs and surgical therapy is still possible should attempts at P.T.A. prove unsuccessful. P.T.A. offers a significant cost advantage as well because it requires only 1-3 days of hospitalization. Dotter and Judkins deserve a great deal of credit for introduction of this procedure which provides potential non-surgical correction of vascular insufficiency for a number of patients.

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Meeting Dates for Your Calendar...

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Winter Scientific Meeting

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The Clinical Utility of M-Mode Echocardiography in the Evaluation of Cardiac Disorders

ROBERT P. ALLEN, M.D.*

Echocardiography is the science which uses high frequency sound waves or ultrasound to study the structures and dynamics of the heart. Ultrasound was first used by ships to detect submarines and measure the ocean depth and was known as sonar.[1] Since World War II, there have been numerous applications of ultrasound in medicine and echocardiography is one of these applications.

The procedure used to obtain an echocardiogram is non-invasive, painless, and may be repeated as often as is necessary. A transducer which emits ultrasound is placed on the patients chest in the 3rd or 4th interspace along the left sternal border. The ultrasound beam travels through the body until it reaches an interface where the density of the tissue changes, such as between the wall of the left ventricle and the blood in the left ventricular cavity. At this point, some of the beam is reflected back towards the transducer and the remainder proceeds on further into the body. The sum of the various reflections from the interfaces encountered is relayed by the transducer to an oscilloscope. When the signal is recorded in a continuous manner overtime, it is called M-Mode Echocardiography. The transducer can be angled and the beam will travel in a different direction and other portions of the heart can then be recorded.

When Edler and his colleagues first began studying echocardiography, they did not know what structures the various patterns of reflections represented. The first echo that was identified was that which originated from the anterior leaflet of the mitral valve.[2] This remains the easiest landmark to locate and is the initial focus of every examination. Feigenbaum[1] and Gramiak[3] and others led the way in determining what structures the reflected echoes represented and correlated differences in these reflections from normal with cardiac disorders.

An example of a normal echocardiogram done with the transducer angled to transect the left ventricle below the level of the mitral valve is shown in Figure 1. The uppermost portion represents the echoes obtained from the chest wall and the anterior wall of the right ventricle. A separation between these structures is not normally present. The right ventricular cavity lies below these echoes. The next structure is the interventricular septum, followed by the left ventricular cavity and the posterior left ventricular wall. A space is not normally seen between the epicardium and pericardium. The most posterior

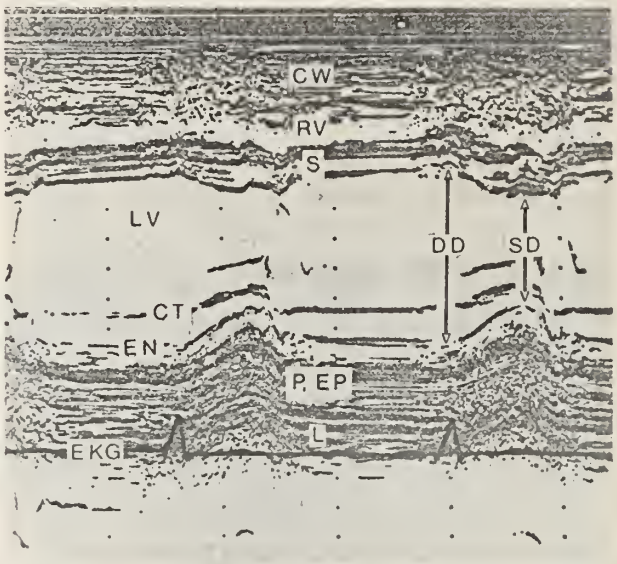


Fig. 1. A normal echocardiogram transecting the left ventricle below the level of the mitral valve. CW = Chest Wall, RV = Right Ventricle, S = Septum, LV = Left Ventricle, DD = Diastolic Dimension, SD = Systolic Dimension, CT = Chordae Tendinae, EN = Endocardium, P,EP = Pericardium, Epicardium, L = Lung, EKG = Electrocardiogram.

echoes at the bottom of the figure come from the lung behind the heart.

In the normal situation where the right ventricle is not dilated or hypertrophied, the septum functions as though it were part of the left ventricle, and the septum and the posterior wall move towards each other in systole and separate in diastole.[4]

The echocardiogram is useful in determining the size of the right and left ventricular chambers, and the thickness of the septum and posterior wall. It is also valuable in determining the functional state of the left ventricle. The end diastolic and peak systolic dimensions can be used to estimate the left ventricular ejection fraction.[5] In the absence of segmental dysfunction from coronary artery disease, the estimated ejection fraction correlates well with that obtained at angiography.

The first valve identified by echocardiography was the mitral valve.[2] The distinctive pattern of a normal mitral valve is shown in Figure 2 in which the transducer has been angled to transect the left ventricle at the level of the mitral valve. In systole, the anterior and posterior leaflets lie close together and gradually move together in an anterior direction. In diastole, as the valve opens at point D, the leaflets separate and rapidly move apart. The point of max-

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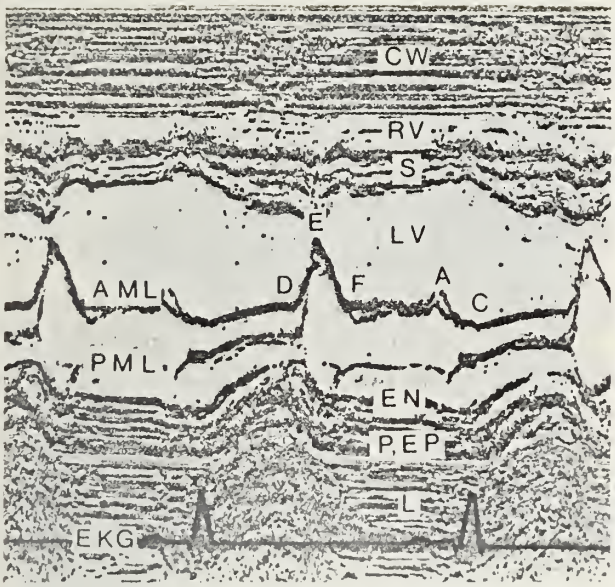


Fig. 2. A normal echocardiogram through the left ventricle at the level of the mitral valve. CW = Chest Wall, RV = Right Ventricle, S = Septum, LV = Left Ventricle, AML = Anterior Mitral Leaflet, PML = Posterior Mitral Leaflet, D = Opening point of Mitral Valve, E = Point of Maximum Opening of Mitral Valve, F = Point where rapid diastolic filling stops and slow filling continues, A = Increased opening of the Valve due to Atrial Contraction, C = Closure of the Mitral Valve, EN = Endocardium, P,EP = Pericardium, Epicardium, L = Lung.

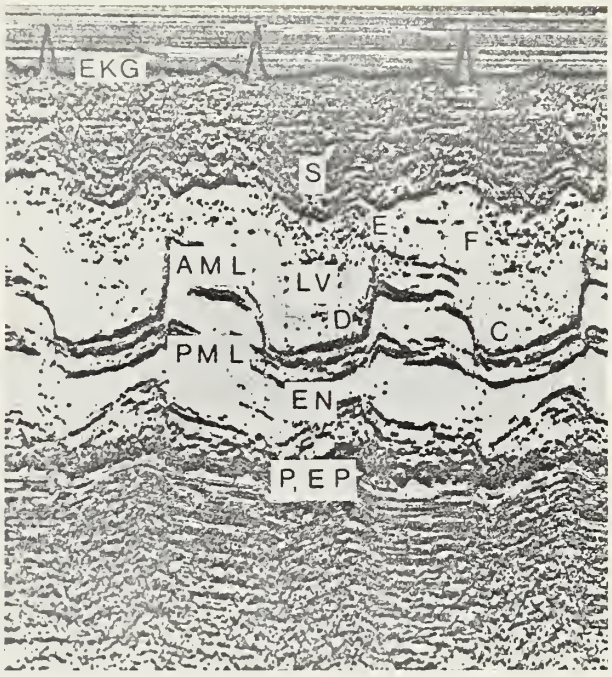


Fig. 3. Echocardiogram of a patient with Mitral Stenosis. S = Septum, LV = Left Ventricle, AML = Anterior Mitral Leaflet, PML = Posterior Mitral Leaflet, D = Point of Mitral Opening, E = Point of Maximal Opening of Mitral Valve, F = End of Diastolic Filling, Beginning of Valve Closure, C = Closure of the Mitral Valve, EN = Endocardium, P,EP = Pericardium, Epicardium.

imal opening with rapid early filling of the ventricle is shown at point E. The leaflets then move towards each other as the valve starts to close. Rapid diastolic filling ends at point F and slow filling continues. Atrial contraction at point A forces the leaflets further apart before closure finally occurs at point C.[6]

The first clinical use of echocardiography was making the diagnosis of mitral stenosis. The disorder markedly changes the pattern of echoes that return from the mitral valve apparatus. Figure 3 shows an example of this. The leaflets of the valve are thickened. The posterior leaflet, which normally moves in a posterior direction in diastole, moves instead in an anterior direction along with the anterior leaflet. This is the case in almost all patients with mitral stenosis. In addition the closure slope (EF slope) after the point of maximal opening (E point) is slow and the A wave or effect of atrial contraction is not seen.[7] Although the actual degree of severity of mitral stenosis cannot be determined, an assessment of the mobility of the valve can be made. If the opening amplitude of the valve (D-E) is 20 mm. or more, a commissurotomy will probably be surgically feasible.[8]

The echocardiogram is extremely useful in making the diagnosis of mitral valve prolapse. The frequency of this disorder which is also termed the "floppy mitral valve syndrome" was not appreciated until the advent of echocardiography. The most common cause is myxomatous degeneration of the valve,

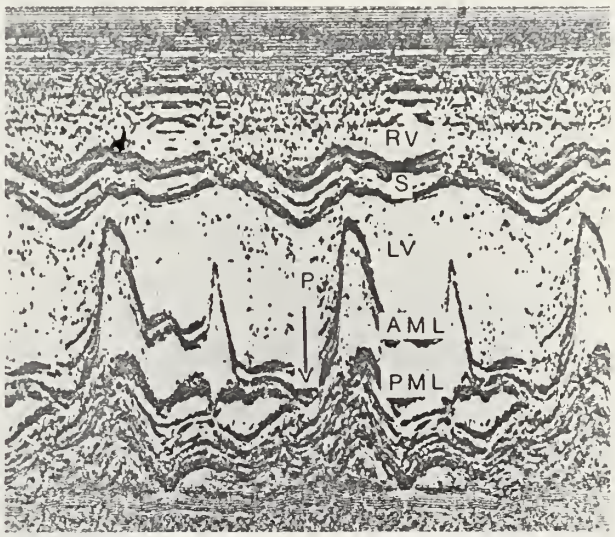


Fig. 4. Echocardiogram of a Patient with Mitral Valve Prolapse, RV = Right Ventricle, S = Septum, LV = Left Ventricle, AML = Anterior Mitral Leaflet, PML = Posterior Mitral Leaflet, P = Prolapse of Posterior Leaflet.

which results in enlargement of the area of the valve leaflets. During systole they will prolapse into the left atrium and this frequently causes an audible mid-systolic click. The disorder is commonly associated with atypical chest pain and occasionally with supraventricular and ventricular arrhythmias. A typical example of mitral valve prolapse is shown in Figure 4. Note that in systole the anterior and posterior leaflets move anteriorly during the beginning of systole, but

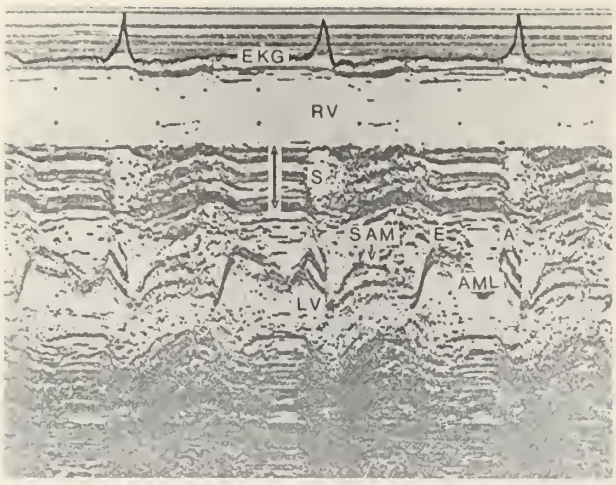


Fig. 5. Echocardiogram of a Patient with Idiopathic Hypertrophic Subaortic Stenosis. RV = Right Ventricle, S = Septum, LV = Left Ventricle, SAM = Systolic Anterior Motion of Mitral Valve, AML = Anterior Mitral Leaflet in Diastole, E = Point of Maximal Mitral Valve Opening, A = Effect of Atrial Contraction to Reopen Mitral Valve Just Before Closure.

in late systole the posterior leaflet suddenly moves in a posterior direction (P). The anterior leaflet may prolapse as well. In other cases both leaflets will start to prolapse at the beginning of systole, and the prolapse will be considered holosystolic.[9,10] The extreme form of this syndrome, a flail mitral leaflet usually due to ruptured chordae tendinae, also has characteristic features.[11]

Another syndrome in which the echocardiogram is virtually diagnostic is in idiopathic hypertrophic subaortic stenosis or hypertrophic cardiomyopathy. The prevalence of this disease was also not appreciated until the advent of echocardiography. The symptoms of the syndrome include dyspnea, angina, syncope and sudden death. Although a systolic murmur is usually present, the correct diagnosis is often clinically unsuspected.

Figure 5 illustrates the typical findings on the echocardiogram. The septum is markedly thickened and the ratio of septal to posterior wall thickness exceeds 1.3 to 1. The mitral valve opening in diastole (E point) abuts very close to the septum. In systole, the anterior mitral leaflet moves suddenly in an anterior direction. This is termed SAM or systolic anterior motion of the mitral valve. When both asymmetic septal hypertrophy and systolic anterior motion of the mitral valve are found, one is highly certain that hypertrophic cardiomyopathy is present.[12,13]

If the transducer is angled medially and superiorly, the ultrasound beam will transect the aorta and left atrium. Figure 6 is a normal echocardiogram with the transducer position moved to visualize the right ventricular outflow tract, aorta, and left atrium. The aortic valve is seen within the aorta. In diastole, a single fine line is present. In systole, the valve opens forming a box like structure. When the aortic valve is abnormal or calcified, the leaflets will be thickened and the box like structure may not be seen at all.

Continued on Page 325

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WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle, the patient should therefore be cautioned accordingly. *Drug Dependence*. Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy*. Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children*. Tenuate is not recommended for use in children under 12 years of age.
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ADVERSE REACTIONS: *Cardiovascular*: Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System*: Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal*: Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic*: Urticaria, rash, ecchymosis, erythema. *Endocrine*: Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System*: Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous*: A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.
DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride): One 25 mg. tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg. tablet daily, swallowed whole, in midmorning. Tenuate is not recommended for use in children under 12 years of age.
OVERDOSAGE: Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phentolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product Information as of April, 1976

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References: 1. Citations available on request—Medical Research Department, MERRELL RESEARCH CENTER, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M.T., O'Dillon, R.H., and Leyland, H.M. A Comprehensive Review of Diethylpropion Hydrochloride. International Symposium on Central Mechanisms of Anorectic Drugs, Florence, Italy, Jan. 20-21, 1977.

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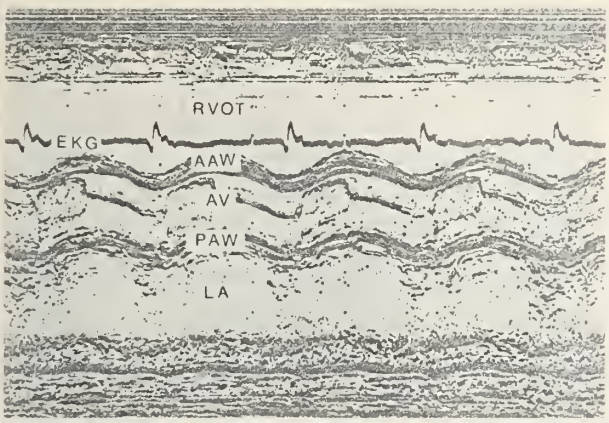


Fig. 6. Normal Echocardiogram through aorta and left atrium, RVOT = Right Ventricular Outflow Tract, AAW = Anterior Aortic Wall, AV = Aortic Valve, PAW = Posterior Aortic Wall, LA = Left Atrium.

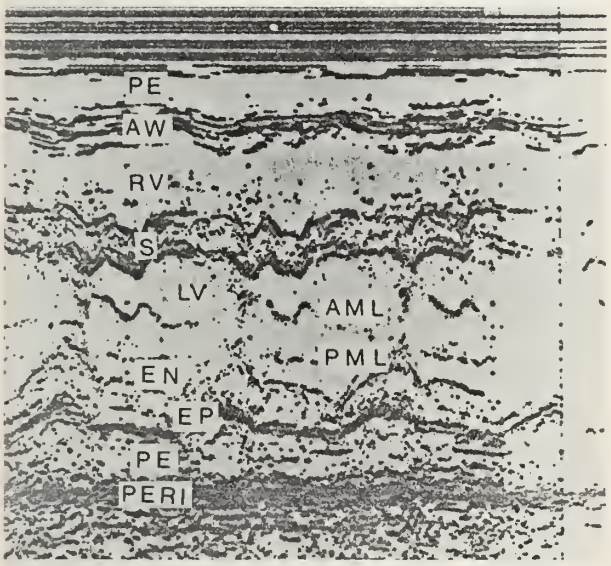


Fig. 7. Echocardiogram of a patient with a moderate sized pericardial effusion. PE = Pericardial Effusion, AW = Anterior Wall of Right Ventricle, RV = Right Ventricle, S = Septum, AML = Anterior Mitral Leaflet, PML = Posterior Mitral Leaflet, EN = Left Ventricular Endocardium, EP = Epicardium, PERI = Pericardium, LV = Left Ventricle.

Although the valve can be diagnosed as being abnormal, the presence or absence of stenosis of the valve cannot be determined.[14] However, in children and perhaps in adults with normal left ventricular function, the pressure in the left ventricle can be estimated using the left ventricular posterior wall thickness and systolic dimension.[15,16]

The echocardiogram is also the most accurate noninvasive tool to estimate the size of the left atrium and is superior to the chest x-ray and electrocardiogram in this regard.[17]

Echocardiography has provided an excellent tool for diagnosing the presence of pericardial effusion. The size of the effusion can be estimated and significant changes in its size can be detected with serial examinations.[18] Figure 7 is an echocardiogram from a patient with a moderate sized pericardial effusion. Note the relatively echo free space between the anterior wall of the right ventricle and the chest wall and between the epicardium of the posterior wall and the pericardium. These spaces represent the presence of the effusion and the size of the spaces correlate with the size of the effusion.

Echocardiography is useful in many other situations. Left atrial myxoma which clinically may present like mitral stenosis can be identified.[19] Other cardiac tumors are visualized as well.

Vegetations from infective endocarditis can be visualized if they are large, and their presence usually connotes that valve damage is severe and replacement is more likely to be necessary.[20]

Abnormalities of the tricuspid valve such as tricuspid stenosis and Ebstein's anomaly can be diagnosed.[21] The pulmonic valve echogram has characteristic features in pulmonic stenosis, infundibular stenosis, and pulmonary hypertension.[22]

Echocardiography is extremely valuable in evaluating and managing patients with congenital heart disease.[23] Ebstein's anomaly,[21] endocardial cushion defect, tetralogy of Fallot, secundum atrial septal defect,[24] hypoplastic left heart syndrome, and many others have characteristic features.

The primary limitation of M-mode echocardiography is that it is not always technically possible to obtain a quality echocardiogram in elderly patients or patients with obstructive airway disease. Bone or calcified tissue will absorb or reflect almost all ultrasound energy. Elderly patients often have a great deal of calcification in the intercostal spaces which can make the examination very difficult. Ultrasound also does not penetrate lung tissue. In patients with hyperinflated lungs due to obstructive airway disease, lung tissue may be present between the transducer and the heart in expiration and prevent the ultrasound beam from reaching the heart.

In the vast majority of patients, however, M-mode echocardiography is a powerful safe, non-invasive diagnostic tool which requires little time and expense. It is also ideally suited for objective periodic assessment of the progress of many cardiac disorders.

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Psoriatic Arthritis

Sidney R. Block, M.D.*

There is a significant association of inflammatory arthritis with psoriasis which cannot be explained by the mere coincidence of common illnesses such as psoriasis, rheumatoid arthritis and/or gout.

Incidence: Psoriasis affects approximately 2 percent of the total population and thus there are presumed to be about 4 million cases in the United States, 20,000 of which are in Maine. Inflammatory arthritis affects about 5 percent of patients who have psoriasis; thus, there are approximately 200,000 cases of psoriatic arthritis nationwide and 1,000 of these cases reside in the State of Maine.

Epidemiology and Genetics: Since the etiology of psoriatic arthritis is unknown and the pathogenesis poorly defined, our attention has been directed to the epidemiology and genetics of the illness for various clues. It is apparent that the severity of psoriasis in some way relates to the incidence of the arthritis for if the psoriasis is severe enough to require hospitalization, then (instead of 5 percent) 30 or 40 percent of these patients have clinical or radiologic evidence of rheumatologic illness. On the other hand, some patients present with severe arthritis without readily apparent psoriasis or only an admission of "dandruff" on careful questioning. Psoriatic arthritis is similar to rheumatoid arthritis in age distribution, but the sex ratio is 1:1, male:female, which is distinctly dissimilar. Furthermore, psoriasis seems to have a significant hereditary component which at best is weak in rheumatoid arthritis. There is a 60 percent concordance of psoriasis in monozygotic twins. Of first degree relatives of patients with psoriatic arthritis, 20 percent have psoriasis, 15 percent have arthritis, and 5 percent have psoriatic arthritis. Histocompatibility factors reveal differences between the two illnesses. HLA-DW4 (Human Lymphocyte Histocompatibility Antigen) may be of some importance in rheumatoid arthritis, whereas HLA-13 and 17 (Human Lymphocyte Histocompatibility Antigen) may have an increased frequency in patients with psoriasis (and perhaps the peripheral type of psoriatic arthritis). However, there is a definite association of HLA-B27 (Human Lymphocyte Histocompatibility Antigen) with the spondylitic type of psoriatic arthritis. Between ⅓ and ⅔ of psoriatic patients with sacroiliitis carry the B27 marker. Looking at it the other way, ⅕ of patients with psoriatic arthritis who are known to have the B27 marker are then found to have sacroiliitis. This may be compared with the 95 percent of patients with ankylosing spondylitis who carry the B27 marker. One concludes that B27 is important in the spondylitis associated with psoriasis, but not as important as in ankylosing spondylitis, and other factors must therefore be of importance in the psoriatic illness.

Pathology: The histology of the synovitis of psoriatic arthritis is the same as rheumatoid arthritis, but the fact that it is found in DIP joints and sacroiliac joints makes the difference. Gross pathological differences are also relative with respect to rheumatoid arthritis: In psoriatic arthritis there is more impressive bone resorption in addition to destructive lesions but less generalized osteoporosis. There is also more marginal bone overgrowth and more periostitis. No rheumatoid nodules are found.

Clinical Features: Although the onset of arthritis generally occurs after a long (average 10 years) history of psoriasis (85 percent), it may occur with the onset of psoriasis (10 percent), and rarely may occur before psoriasis can be found (5 percent). The arthritis is of an acute onset in approximately 40 percent of patients. According to the literature, exacerbations and remissions of the skin and joint disease may be synchronous in approximately 50 percent of patients. My experience would indicate a lesser correlation. Articular remissions tend to be more frequent, rapid and complete than in rheumatoid arthritis; but, on the other hand, psoriatic arthritis may be an even more mutilating illness than its rheumatoid relative.

Psoriatic arthritis may present in 5 recognized patterns: 70 percent of patients develop asymmetric oligoarthritis primarily affecting large joints. Fifteen percent of patients develop a symmetrical polyarthritis. The arthritis may be limited to DIP joints and associated with psoriasis of the nails (5 percent); limited to spondylitis (5 percent); or progress unrelentingly to a mutilans form with severe osteolysis (5 percent). Overlaps of these patterns are frequent. DIP involvement may occur in either the asymmetric or symmetric forms. Spondylitis is very frequent in the mutilans form and overall occurs in ⅓ of patients. An impressive clinical finding is dactylitis (sausage digit). This diffuse swelling of an entire finger seems to be primarily an arthritis of the PIP joint with flexor tendon sheath spread to the DIP and MCP joints.

Systemic manifestations are infrequent but important: Iritis occurs in about 7 percent of patients and is associated with the B27 antigen, spondylitis, deforming illness, and male sex. Other eye involvement includes conjunctivitis, episcleritis, and sicca syndrome. Aortic insufficiency when it occurs is related to aortitis. Fever has been reported with severe polyarticular flares. Amyloidosis of the gastrointestinal tract has been reported (but fortunately as yet not observed by myself).

Laboratory: The RA latex is negative. Elevations of sedimentation rate and gammaglobulins, and ane-

*412 State Street, Bangor, Maine 04401

mia reflect acute and chronic inflammation. Hyperuricemia occurs in 10 to 20 percent of patients with psoriasis and reflects the rapid tissue turnover of extensive skin disease. As noted above, HLA-B27 is associated with those patients who have sacroiliitis.

Radiology: The characteristic radiologic findings in psoriatic arthritis are as follows: Erosion of terminal phalangeal tufts (acro-osteolysis); whittling and cupping (pencil in cup deformity); bony ankylosis of joints; asymmetry of large and small joint involvement; severe destruction of isolated small joints; predilection for DIP joints; asymmetric sacroiliitis; fluffy periostitis; and mutilans (which is a severe combination of erosive and osteolytic destructive disease).

Differential Diagnosis: In those 95 percent of patients who already have psoriasis, the question generally is limited to whether or not the patient has psoriatic arthritis or some other type of superimposed inflammatory arthritis. In those 5 percent of patients who do not present with defined psoriasis, the differential diagnosis is more difficult and the exact nature of the condition may remain obscured for some time. If the rheumatoid factor is persistently and strongly positive, then the diagnosis is assumed to be rheumatoid arthritis superimposed upon psoriasis (or possibly coexistent rheumatoid arthritis and psoriatic arthritis). This raises the question of whether the seronegative polyarthritis associated with psoriasis might not also, in fact, be seronegative rheumatoid arthritis. There is no way to tell, and the problem is not merely semantic since the treatment for the two types of arthritis may differ. Psoriatic arthritis may have a gout-like onset and, as noted above, 20 percent may have hyperuricemia. To help confuse the clinician, some of these patients respond to colchicine. The diagnosis may depend upon aspiration of monosodium urate crystals from the affected joint. It may be impossible to differentiate coexisting ankylosing spondylitis or Reiter's syndrome. Extensive spinal disease and symmetrical sacroiliitis suggest ankylosing spondylitis. However, in Reiter's syndrome keratodermia blenorrhagica is identical to pustular psoriasis and the associated sacroiliitis frequently is also asymmetrical. Radiographically defined osteolysis helps differentiate psoriasis with DIP involvement from erosive osteoarthritis. The difficulty in differential diagnosis and the existence of so many forms of inflammatory arthritis associated with psoriasis has led to the hypothesis that psoriatic arthritis represents an important intersection of the rheumatic illnesses. Certainly the striking "coincidences" deserve further investigation.

Treatment: It is important to treat the skin lesions of psoriasis for it is possible that the activity of the arthritis may synchronously improve. Physical measures of care, occupational therapy, and education play important roles in this chronic illness. Historically, Indocin® and Butazolidin® have been the medications of choice. Nonetheless, aspirin may still be a safer long term first choice if effective. The use of Clinoril® , Motrin® , Nalfon® , Tolectin® , and Naprosyn® are as yet not "approved" for use in psoriatic arthritis, but I prefer to take my chances with the FDA rather than with Butazolidin whenever possible. Some investigators have found gold therapy or Plaquenil® to be helpful for psoriatic arthritis. The use of these medications is not generally recognized by rheumatologists and the danger of serious flares of the psoriatic skin condition merits circumspection. Joint injections are useful when one or a few joints fail to respond to other medications. Systemic steroids are generally avoided, but I still prefer their use to cytotoxic drugs when only the arthritis is taken into consideration. I have less qualms when Methotrexate, Purinethol® , Imuran® , or Hydrea® have been independently deemed necessary by a dermatologist. It is of interest that the response of the skin and joint manifestations to these cytotoxic drugs may not be synchronous. One always worries about their serious side effects, including the long term potential for malignancy. Surgical considerations for psoriatic arthritis are similar to rheumatoid arthritis and both synovectomy and reconstructive surgery fall within the therapeutic regimen.

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Is the Buchwald Operation Underutilized?

David M. Sensenig, M.D.*

Arteriosclerosis with focal symptomatic lesions occurring in a relatively young person is of especial importance because of the otherwise long life expectancy. We had the opportunity to perform femoropopliteal venous bypass grafts in a fifty-year-old man with hyperlipidemia. We wished to diminish the chance of further arteriosclerotic complications.

Case Report

A fifty-year-old man was seen in 1976 because of intermittent claudication in both calves worse on the right side. Arteriography showed 90% occlusion of the distal common femoral artery on the right and 60% on the left plus complete occlusion of both superficial femoral arteries. He could only walk 100 to 200 feet at the most. He smoked one and one-half packs of cigarettes a day and did not use alcohol. He had a Type IV (Frederickson) hyperlipidemia and had been on a low cholesterol, low carbohydrate, low saturated fat diet. There were no cardiac symptoms.

On physical examination, his blood pressure was 120/80. He had strong femoral pulses bilaterally with no distal pulses.

An ECG showed ST and T wave changes of minor degree. A chest x-ray was normal. Cholesterol was 597 mg. percent, triglycerides were 2560 mg. percent and glucose was 130 mg. percent. T4, T3, and FTI showed normal thyroid function.

On 6-28, a bypass vein graft from the common femoral to popliteal artery plus excision of a small popliteal artery aneurysm was done on the right with restoration of good ankle and foot pulses. He developed a postoperative deep phlebitis which required maintenance Coumadin® therapy.

The patient was readmitted in January, 1977 because of severe claudication on the left. He was allegedly following the low carbohydrate, low saturated fat and low cholesterol diet. Six months previously his cholesterol was 636 mg. percent and triglycerides were 2306 mg. percent with milky plasma. He was known to have an enlarged liver.

On examination, the liver was palpable 7 cm. below the right costal margin. There was a good pulse at the right ankle but no pulses below the left femoral.

Cholesterol was 568 mg. percent and triglycerides 2400 mg. percent. A left femoral artery to popliteal artery bypass vein graft was performed on the left restoring a good left ankle pulse.

The patient was admitted to St. Joseph Hospital in December, 1977 for an ileal bypass (Buchwald) operation. Despite medical management by his internist over a four-year period, using diet and clofibrate for one year, his cholesterol was 792 mg. percent and triglycerides were 4226 mg. percent with milky serum. He had developed painful subcutaneous xanthomas on both hands and feet. He had diarrhea since cholecystectomy averaging 1 to 3 stools a day.

On examination, he had good posterior tibial pulses bilaterally and xanthomas on both hands and feet.

His cholesterol was 522 mg. percent.

On 12-7-77, a Buchwald operation was done bypassing 200 cm. of terminal ileum which about divided the small bowel into two equal lengths.

On 12-18-77, his cholesterol was 154 mg. percent and triglycerides were 475 mg. percent. On 2-2-78, his cholesterol was 196 mg. percent and triglycerides were 583 mg. percent with pre-beta lipoproteins elevated in a manner suggestive of Type IV hyperlipidemia.

Postoperatively the patient lost weight from 179 pounds to 155 pounds and later gained to 162 pounds. His height is 66 inches. In December, 1978, a year after ileal bypass, his cholesterol was 176 mg. percent and triglycerides were 600 mg. percent. In November, 1978 he had three small kidney stones which caused some short lived pain. In April, 1979 his cholesterol was 222 mg. percent and triglycerides were 690 mg. percent. At the present time the patient feels well. Since his triglycerides are still elevated, we try to keep him on his diet. He has about 5-6 stools a day.

Discussion

It is generally accepted today based on epidemiologic studies that the level of circulating cholesterol is a major indication of atherosclerotic risk. National clinical trials are in progress to test the efficacy of prolonged lipid lowering. While awaiting the results which will require another ten years or so, it seems wise to utilize lipid reduction.

In 16 studies, dietary methods provided an average reduction of 13 percent in the cholesterol level with a 6 percent reduction in the control group.

Therapy with drugs such as cholestyramine, clofibrate, and nicotinic acid do not reduce cholesterol more than 23 percent.

Buchwald demonstrated that bypass of the distal third of the small bowel interferes with the enterohepatic bile acid cycle and results in a loss of bile acid in the feces three times normal. The bypass places a direct drain on the body cholesterol pool and an indirect drain through conversion of cholesterol to bile acids in order to maintain the bile acid reservoir. Partial ileal bypass in rabbits will prevent hypercholesterolemia and atherosclerosis in animals fed an atherogenic (2 percent cholesterol) diet for four months. Adaptive mechanisms do not lead to a later return to high cholesterol blood levels. Similar results have been obtained in dog and monkey.

About 250 Buchwald operations have been performed at the University of Minnesota up to this time. Circulating cholesterol has been reduced in these patients by about 40 percent. In Type IV hyperlipoproteinemia triglyceride reduction after ileal bypass has averaged 53 percent in Buchwald's series.

Diarrhea is sometimes annoying. Ninety percent of patients have less than 5 bowel movements a day after one year. Vitamin B12 (1000 micrograms) is given intramuscularly every two months. In general, arthritic phenomena, nephrolithiasis, formation of gallstones and fatty liver have not been caused by partial ileal bypass. Xanthomas have decreased in size or disappeared. Sixty-six percent of patients with angina preoperatively experienced improvement. It is of interest that high cholesterol content reduces oxygen extraction from blood.

Summary and Conclusion

A case of a 50-year-old man with atherosclerotic femoral artery occlusions and Type IV hyperlipidemia refractory to dietary management is presented.

*From the Surgical Services, Eastern Maine Medical Center and St. Joseph Hospital, Bangor, Maine 04401.

A high blood cholesterol was reduced to normal and triglycerides were reduced to 25 percent of the preoperative value by Buchwald's partial ileal bypass.

In the analyzed results of Buchwald's and other series, cholesterol has been reduced 40 percent from the level achieved after dietary therapy.

The question is raised whether the Buchwald operation should not be performed more often in those patients with high cholesterol levels despite dietary therapy. Perhaps many cases of coronary occlusion and atherosclerotic peripheral arterial complications could be prevented.

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Title: **State of Maine Academy of Family Physicians Annual Meeting—Scientific Session**
Date: December 1, 1979
Location: Portland, Maine
Sponsor: State of Maine Academy of Family Physicians
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Hospital Activities

Augusta General Hospital
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August 28, 1979 **Ophthalmology Conference**
7:30-8:30 a.m. William E. Atlee, M.D., AGH
Robert Takach, M.D., MMMC

September 25, 1979 **Visiting Professor—Endocrinology**
7:30-9:30 a.m. Burritt Haag, Tufts University School of Medicine

Programs have been certified AMA Category I and AAFP (prescribed). For further information contact Mrs. Nancy York; 623-4711. Programs may be viewed over ITS.

Augusta Mental Health Institute
Augusta, Maine

September 13 **Emergency Assessment of Depression** 10-11:30 a.m.
Hypochondriasis 1:30-3 p.m.
George B. Murray, M.D., Harvard Medical School

September 20, **Childhood Depression** 10-11:30 a.m.
Anorexia Nervosa 1:30-3 p.m.
David Herzog, M.D., Harvard Medical School

October 4 **Issues in Geriatric Psychiatry I: Normal and Pathological Behavior in the Elderly** 10-11:30 a.m.
Issues in Geriatric Psychiatry II: Depression, Dementia and Paranoia 1:30-3 p.m.
Kenneth Nobel, M.D., Harvard Medical School

October 18 **The Therapeutic Contract** 10-11:30 a.m.
1) Analysis of Resistance 1:30-3 p.m.
2) The Termination Triad
Edward Messner, M.D., Harvard Medical School

The 10-11:30 a.m. Sessions are Grand Rounds; 1:30-3 p.m. Sessions are Inpatient Psychiatry Courses. All programs have been certified AMA Category I. For further information contact Pauline H. Soper; 622-3751.

Dean Hospital
Greenville, Maine

Sept. 21 **Pediatrics & Pediatric Cardiology**
9:30a.m.-Noon Dorothy Eisengart, M.D., MMMC

This program has been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621

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Every Mon.	Surgical Service—Chief's Rounds	5-6 p.m.
4th Mon.	ENT Section Meeting	12-1 p.m.
4th Mon.	Neurosurgery Section Meetings	4-5 p.m.
3rd Tues.	Dermatology-Pathology Conference	5-6 p.m.
3rd Tues.	Dermatology Section Meeting	6-7 p.m.
4th Tues.	Pulmonary Medicine Section Meeting	8-9 a.m.
1st Wed.	Hematology/Oncology Meeting	8-9 a.m.
Every Wed.	Tumor Clinic Conference	2-5 p.m.
Every Wed.	Radiology Conference (1) Ultrasound/Nuclear Medicine (2) Radiology Film Review (3) Neuroradiology (4) Teaching File Conference	5-6 p.m.
1st Thurs.	Ophthalmology Section Meeting	7:30-8:30 a.m.

	OB-GYN Conference (1) Pathology (2) GYN Analysis (3) OB-Pediatric Combined (4) In-Service and Education	8-9 a.m.
Every Thurs.	Pediatric Grand Rounds	9-10 a.m.
Every Thurs.	Medical Service Conference	10-11 a.m.
Every Thurs.	Cardiology Conference	11 a.m.-1 p.m.
2nd Thurs.	Orthopedic Grand Rounds	7:45-8:45 a.m.
4th Thurs.	Orthopedic Service Meeting	7:30-9 a.m.
4th Thurs.	Surgical Service Death Review	7:45-8:45 a.m.
Every Thurs.	Psychiatric Service Grand Rounds	10-11 a.m.
4th Thurs.	Urology Section Conference	7:30-8:30 a.m.
Every Fri.	Neurology Grand Rounds	8-9 a.m.

Visiting Professor Program:

2nd Thurs.	Medical Service Visiting Professor	10 a.m.-5 p.m.
2nd Thurs.	Anesthesia Service Visiting Professor	7-8 a.m.
3rd Thurs.	OB/GYN Service Visiting Professor	10 a.m.-4 p.m.
Saturdays	Surgery Service Visiting Professor	8 a.m.-Noon
4th Thurs.	Pediatric Service Visiting Professor	10 a.m.-5 p.m.
as scheduled	Orthopedic Service Visiting Professor	
as scheduled	Family Practice Visiting Professor	
as scheduled	Psychiatric Service Visiting Professor	
as scheduled	Radiology Service Visiting Professor	

All activities have been certified AMA Category I. For further information contact Robert H. Brown, M.D., Chairman, Medical Education Committee; 947-3711, Ext. 330.

Franklin County Hospital
Farmington, Maine

September 10, 1979 **Oncology Conference**
6-8:30 p.m. Joseph Hiebel, M.D., MMMC
Donald Magioncalda, M.D., AGH

September 19, 1979 **Visiting Professor—Cardiovascular Disease**
12 Noon-2:30 p.m. Shapur Naimi, M.D., New England Medical Center in Boston

All activities have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621.

Maine Medical Center
Portland, Maine

Every Mon.	Student Technologist Conference	8 a.m.
Every Mon.	Hematology Pathology Conference	11 a.m.
Every Mon.	Pulmonary Conference	12 Noon
Every Mon.	Pediatric Residents Conference	1 p.m.
Every Mon.	Anesthesia Formal Resident Lecture	3:30 p.m.
Every Mon.	Surgical Pathology Review	4 p.m.
Every Mon.	Radiology Journal Club	5 p.m.
1st & 3rd Mon.	Clinical Nephrology Conference	11 a.m.
1st & 3rd Mon.	Hematology-Pathology Conference	12 Noon
3rd Mon.	Eye Conference	11:45 a.m.
Every Tues.	Radiology Residents' Seminar	a.m.
Every Tues.	Family Practice Grand Rounds	9 a.m.
Every Tues.	Electrocardiographic Interpretation	1 p.m.
Every Tues.	Psychiatric Grand Rounds	1:30 p.m.
Every Tues.	Anesthesia Formal Resident Lecture	3:30 p.m.
Every Tues.	Surgical Seminar	4 p.m.
Every Tues.	Pathology Slide Seminar	4 p.m.
1st & 3rd Tues.	Radiology Pathology Conference	12 Noon
1st & 4th Tues.	Neurology Conference	12 Noon
2nd Tues.	Infectious Disease Conference	12 Noon
3rd Tues.	Hematology Conference	12 Noon
5th Tues.	Oncology Conference	12 Noon
Every Wed.	Radiation Therapy Conference	7 a.m.
Every Wed.	Urology Conference	7 a.m.
Every Wed.	Student Technologist Conference	8 a.m.
Every Wed.	Continuing Education Seminar	8 a.m.
Every Wed.	Medical Conference	9 a.m.
Every Wed.	Psychiatric Journal Club	12 Noon
Every Wed.	Cardiology Seminar	12 Noon
Every Wed.	Surgical Grand Rounds	5 p.m.
2nd Wed.	Guest Internist—Medical Conference	9 a.m.
4th Wed.	Medical Mortality Conference	9 a.m.
Alt. Wed.	Neurology—Psychiatry Seminar	11 a.m.
Alt. Wed.	Anesthesiology Journal Club	3 p.m.
Every Thurs.	Thoracic Surgery Conference	7 a.m.
Every Thurs.	OB/GYN Conference	7 a.m.
Every Thurs.	Anesthesiology Clinical Conference	7 a.m.
Every Thurs.	Diagostic Radiology Teaching Conference	7 a.m.
Every Thurs.	Surgical Conference	8 a.m.
Every Thurs.	Pediatric Conference	9 a.m.
Every Thurs.	Tumor Consultation Board	11 a.m.
Every Thurs.	Medical Resident Conference	12 Noon
Every Thurs.	Surgical Seminar	4 p.m.
Every Thurs.	Endocrinology Conference	5 p.m.
Every Thurs.	Dental Specialty Lecture	6 p.m.
1st Thurs.	Anesthesia Mortality Conference	7 a.m.
1st Thurs.	Guest Pediatrician	9 a.m.
1st & 3rd Thurs.	Gastroenterology Conference	12 Noon
1st & 3rd Thurs.	Cardiac-Surgical Conference	12:30 p.m.
1st, 3rd, & 5th Thurs.	Pulmonary Physiology Conference	12:30 p.m.
2nd Thurs.	Cardiology Teaching Conference	12:30 p.m.
2nd Thurs.	Clinical Anesthesiology Lecture Series	3:30 p.m.
2nd Thurs.	Eye Staff Scientific Session	5:30 p.m.
2nd Thurs.	Maine Medical Center Medical Staff Meeting and Scientific Session	6 p.m.
2nd & 4th Thurs.	Pulmonary-Pathology Conference	12 Noon
2nd & 4th Thurs.	Endocrinology Conference	12 Noon
3rd Thurs.	Combined Guest Physician or Guest Surgeon Program	8 a.m.
3rd Thurs.	Clinical Anesthesiology Lecture Series	3:30 p.m.
4th Thurs.	Surgical Mortality Conference	8 a.m.
4th Thurs.	Anesthesia Mortality Conference	3:30 p.m.
Last Thurs.	Pediatric Mortality Conference	9 a.m.
Every Fri.	Thoracic Surgical Conference	7 a.m.
Every Fri.	Nuclear Medicine Conference	7 a.m.
Every Fri.	Student Technologist Conference	8 a.m.
Every Fri.	Neurological Neurosurgical Conference	8:30 a.m.
Every Fri.	Gastroenterology Conference	9 a.m.
Every Fri.	Medical Rehabilitation Staff Conf.	a.m.
Every Fri.	Orthopedic Conference	9 a.m.
1st Fri.	Dermatology Conference	12 Noon
2nd Fri.	Nephrology Conference	12 Noon
3rd Fri.	Rheumatology Conference	12 Noon
4th Fri.	Oncology Conference	12 Noon
Alt. Fri.	Oncology Radiation Conference	7 a.m.
Alt. Fri.	Gastroenterology Conference	10 a.m.

All programs have been certified AMA Category I. For further information contact Costas T. Lambrew, M.D.; 871-2111

Continued on Page 335

Maine Medical Association

STANDING COMMITTEES—1979-1980

Standing Committees for 1979-1980 as proposed by the Committee on Nominations and approved at the Second Meeting of the House of Delegates of the Maine Medical Association at Rockport, Maine, June 17, 1979.

Council on Health Manpower and Education

Committee on Allied Health Professions

Lewis E. Phillips, M.D., 336 Mt. Hope Ave., Bangor 04401 (3 yrs.)—Chairman
Robert G. MacBride, M.D., 25 Washington St., Lubec 04652 (1 yr.)
Buell A. Miller, M.D., 260 Western Ave., So. Portland 04106 (1 yr.)
George L. Pauk, M.D., 77 Prospect St., Portland 04102 (2 yrs.)
A. Dewey Richards, M.D., 180 Main St., Orono 04473 (3 yrs.)
David R. Eitel, M.D., St. Mary's Gen. Hosp., Lewiston 04240 (3 yrs.)

Committee on Continuing Education

Henry J. Wheelwright, M.D., Augusta Gen. Hosp., Augusta 04330 (3 yrs.)—Chairman
Robert H. Brown, M.D., MRC, Box 45, Bangor 04401 (1 yr.)
Costas T. Lambrew, M.D., MMC, Portland 04102 (1 yr.)
Joe R. Wise, Jr., M.D., 417 State St., Bangor 04401 (1 yr.)
David R. Ginder, M.D., Mid-Maine Med. Ctr., Waterville 04901 (1 yr.)
Robert L. Ohler, M.D., Box 58, Winthrop 04364 (1 yr.)
George E. Sullivan, M.D., 100 College Ave., Waterville 04901 (1 yr.)
Michael C. Bach, M.D., 97 Campus Ave., Lewiston 04240 (2 yrs.)
Alfred Hurwitz, M.D., 26 Wood Pond Lane, Kennebunk 04043 (2 yrs.)
James F. Lawsing, III, M.D., 417 State St., Bangor 04401 (3 yrs.)
Carole St. Pierre-Engels, M.D., Washburn Reg. Health Ctr., Washburn 04786 (3 yrs.)
Peter J. Leadley, M.D., Box 706, 99 Western Ave., Augusta 04330 (3 yrs.)

Committee on Recruitment, Aid & Placement

Ferris S. Ray, M.D., 7 Bramhall St., Portland 04102 (1 yr.)—Chairman
Margaret H. Hannigan, M.D., 10 High St., Lewiston 04240 (1 yr.)
Robert E. McAfee, M.D., 7 Bramhall St., Portland 04102 (2 yrs.)
Donald M. Robertson, M.D., Box 188, Milbridge 04658 (2 yrs.)
Charles H. Lightbody, M.D., No. Main St., Guilford 04443 (3 yrs.)
David D. Smith, M.D., CMMC, Lewiston 04240 (3 yrs.)

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Dana M. Whitten, M.D., Med. Bldg., Northport Ave., Belfast 04915 (1 yr.)—Chairman
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Candace C. Walworth, M.D., 97 Campus Ave., Lewiston 04240 (2 yrs.)
David D. Smith, M.D., CMMC, Lewiston 04240 (2 yrs.)
Daniel H. Wood, M.D., 14 Oak Grove, Bath 04530 (3 yrs.)

Council on Medical Services

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Ruth E. Endicott, M.D., Grasshopper Lane, Ogunquit 03907 (1 yr.)
John J. Pearson, M.D., 221 So. 4th St., Old Town 04468 (2 yrs.)
Oram R. Lawry, Jr., M.D., 96 Limerock St., Rockland 04841 (3 yrs.)
Dorothy I. Eisengart, M.D., 325 Kennedy Mem. Dr., Waterville 04901 (3 yrs.)
David C. Dixon, M.D., Rt. 2 & 4, Farmington 04938 (3 yrs.)

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John F. Egan, M.D., RFD #3, Box 37A, Turner Rd., Auburn 04210 (1 yr.)
Frank H. Lawrence, M.D., 22 Bramhall St., Portland 04102 (2 yrs.)
H. Alan Hume, M.D., 295 Water St., Augusta 04330 (2 yrs.)
Thomas V. Brennan, M.D., 106 Hardy St., Presque Isle 04769 (3 yrs.)
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Herbert C. Gilman, M.D., 40 Crestmont Ave., Millinocket 04462 (3 yrs.)

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Francis I. Kittredge, M.D., 498 Essex St., Bangor 04401 (3 yrs.)
Richard C. Leck, M.D., Bath Mem. Hosp., Bath 04530 (3 yrs.)
Richard L. White, M.D., 7 Bramhall St., Portland 04102 (3 yrs.)
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John Kazutow, M.D., Box 113, Columbia Falls 04623 (1 yr.)—(Washington)
Harland G. Turner, M.D., Box 38, Norridgewock 04957 (1 yr.)—(Somerset)
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Continued on Page 333

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Robert B. Keller, M.D., Medical Bldg., Belfast 04915 (3 yrs.)—(Waldo)

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Maine Society of Anesthesiology—George W. Bostwick, M.D., P.O. Box 388, Newcastle 04553
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Maine Neurosurgical Society—Richard M. Swengel, M.D., 477 Main St., Lewiston 04240
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Allan J. Stinchfield, M.D., 16 E. Chestnut St., Augusta 04330

ABSTRACTS
Fifth Annual Maine Biomedical Science Symposium
The University of Maine at Orono
June 14-15, 1979

ADDENDUM (Continued from July 1979 issue)

Human Genetics

Genetic Epidemiology: Its Value in Medical Genetic Service and Research in Maine

T. H. RODERICK and C.H. BUNKER, The Jackson Laboratory and Genetic Counseling Center, Bar Harbor, Maine 04609

Genetic epidemiology is the study of or the attempt to determine the genetic component of etiology, distribution and control of disease. If the genetic component is ascertained, there are significant opportunities for genetic service including precise diagnosis of genetically heterogeneous disorders and the ascertainment of communities or groups of people at high risk for particular genetic disease. The methods of genetic epidemiology may also provide evidence for a genetic basis of sporadic cases of unknown etiology. These methods can be important in proving a common genetic basis for certain disorders with variable expressivity. Maine with its many geographically isolated and genetically closed populations can benefit from a program in genetic epidemiology.

Cell and Molecular Biology

Transplacental Carcinogenesis by Nitrosoureas in the Rabbit

R.R. FOX, B.A. DIWAN, R. POTTATHIL, H.G. BEDIGIAN, and H. MEIER, The Jackson Laboratory, Bar Harbor, Maine 04609

The intraperitoneal administration of a single dose of 1-ethyl-1-nitrosourea (ENU) (60 mg/kg) in trioctanoin to pregnant rabbits, or either strain WH/J or IIIVO, on day 18 of gestation has induced primary renal tumors in the resultant progeny with a mean latency period of about 4 months. In all cases, the tumors were renal tubular cystadenomas, cystadenocarcinomas or nephroblastomas which appeared to develop within small renal cortical cysts. The frequency varied with strain and other genetic factors. Metastases occurred. The oral administration of the precursers ethylurea (100 mg/kg) plus sodium nitrite (50 mg/kg) to pregnant rabbits on days 17, 18, and 19 of gestation induced, by the in vivo formation of ENU, an identical spectrum of primary renal tumors with a similar latency period. To test the effect of low chronic treatment of nitrosoureas pregnant rabbits of strains WH/J and IIIVO/J were given ENU i.p. at a rate of 10 mg/kg/day for ten days. ENU was dissolved in trioctanoin. Regimens were either day 10 through 19, day 15 through 24 or day 18 through 27. Preliminary data revealed both teratogenic and carcinogenic effects following such chronic treatments. A disproportionate stunting or miniaturization was evident, the frequency of which increased with the age of the fetuses when treated. In contrast the parietal bones were found to have holes present at birth, but with their frequency decreasing with increasing fetal age at time of treatment. The spectrum of tumors observed is broader with the chronic regimens and the latency period for primary renal tumors, greater than with the acute dose. (Supported in part by CTR-951, RR-00251 and CP33255).

The Clinical Utility of M-Mode Echocardiography in the Evaluation of Cardiac Disorders

Continued from Page 325

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County Society Notes

Washington

A regular meeting of the Washington County Medical Society was held at the Lincoln Inn, Dennysville on March 13, 1979, with five members and guests present.

Minutes of the last meeting of January 23, 1979 read and approved.

Correspondence:

Dr. James C. Bates, President of the Washington County Medical Society, stated that he had talked and also communicated, by letter, to Marshall Frankel of the Dept. of Health, Education & Welfare, in regard to the Washington County Health Plan.

Dr. Bates stated that the members of the Washington County Medical Society, fourteen, were in favor of the continuance of the present plan, with some modification; nine were in favor of discontinuing the entire plan and five obstained from voting.

It was the general feeling that physicians would be more satisfied with plans, if some type of co-payment could be arranged on the patient's part.

Old Business:

A resolution initiated by the Washington County Medical Society presented to Dr. Francis Kittredge, President of the Maine Medical Association, will apparently come before the House of Delegates at the June meeting of the Maine Medical Association. This resolution asked that each County Society have a member on the Executive Board.

Dr. James C. Bates stated that he would contact David Smith, Commissioner of Maine Human Services, in regard to the delay on reimbursement of Medicare and Medicaid payments.

Dr. Bates also would contact David Smith, Commissioner of Maine Human Services, in regard to "Coding" being done in physician's offices.

Philip and Daynee Orte, Registered Physiotherapists of Machias, Maine, spoke to the Washington County Medical Society about physiotherapy. Mr. and Mrs. Orte are associated with the Counseling Center in East Machias. At present they take care of patients in the nursing homes and patients that are home-bound and are unable to go to the hospital for physiotherapy. Their present territory is approximately all of Washington County. Most of these visits are paid for by Medicare. They take care of patients recovering from accidents; patients recovering from CVA's; cardiac patients following recovery from Myocardial Infarctions, and also patients with Chronic Obstructive Pulmonary Disease. They usually take care of patients in which there is some hope of rehabilitation. The usual method is to evaluate the patient, set up a plan of treatment and then revisit the patient to see if the plan of treatment has been carried out. Home visits are many times repeated, because of inability for any of the people at the home to carry out the plan of treatment. In the nursing homes, however, the nurses and nurses aides, usually are able to carry out their plan of treatment, so it is necessary for them to only make a repeat visit, to find out how the patient is progressing and also to determine when they should be discharged from their care.

Members of the Society were interested in this discussion and asked many questions about their method of treatment.

The meeting adjourned at 9:30 p.m.

KARL V. LARSON, M.D., *Secretary*

Oxford

A regular meeting of the Oxford County Medical Society was held on March 14, 1979 at Tatone's Restaurant, Mexico, with twenty members present.

The meeting was called to order by Dr. H. Richard Bean, President.

The reading of the previous minutes was dispensed with.

Dr. Bean introduced the guest speaker of the evening, Dr. Donna K. Thompson, Medical Oncologist, Central Maine Medical Center, Lewiston. Dr. Thompson presented the recent advances in chemotherapy and a review of tumor response to chemotherapy. Discussion followed this interesting lecture.

Dr. David L. Phillips, Executive Committee Chairman, Maine Medical Association, presented the drawings of the proposed executive offices of the Maine Medical Association in Augusta. Different ideas of low energy concept were included in the drawings submitted by the architects. The total expenditure is expected to be in the range of $250,000. Final bids have been asked for and will be discussed at the Maine Medical Association Annual Assembly in June.

The Secretary-Treasurer informed the Society members that the current checking account balance is $268.18.

The members then adjourned for dinner which was enjoyed by all.

HARBANS S. SODHI, M.D., *Secretary*

CONTINUING MEDICAL EDUCATION IN MAINE

Continued from Page 331

Mid-Maine Medical Center
Waterville, Maine

August 30, 1979 — **Henocult Positive Stool—Carcinoma of the Colon**
12-1 p.m. — Philip Hunter, M.D., EMMC

This program has been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621. This program may be viewed over ITS.

Sebasticook Valley Hospital
Pittsfield, Maine

September 6, 1979 — **Arthritis**
9 a.m.-Noon — Currier McEwen, M.D., Regional Memorial Hospital

All activities have been certified AMA Category I. For further information contact David Ginder, M.D.; 873-0621

Stephens Memorial Hospital
Norway, Maine

September 10, 1979 — **Zebras: Medical Oddities**
Michael A. LaCombe, M.D., Stephens Memorial Hospital

This program has been certified AAFP-2 hours. For further information contact Shelly Wyman; 743-5933

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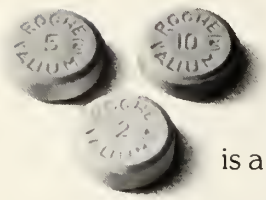
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The Journal
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Volume Seventy | Brunswick, Maine, September 1979 | Number 9

Appendicitis During Pregnancy

Ten-Year Review at MMC

MARK ARANSON, M.D.*

Since 1848, when Hancock[11] reported the first drainage of an appendiceal abscess during pregnancy, subsequent reports have indicated that appendicitis during pregnancy is the most common extrauterine complication of pregnancy requiring surgery and the most common surgical emergency during pregnancy.[10] Also noted, is the fact that appendicitis during pregnancy, especially in the latter months, is potentially a very dangerous disease to both fetus and mother. The experience in recent years, from 1969 through 1978, of all cases with appendicitis during pregnancy at the Maine Medical Center were compared with reports from elsewhere in the United States, Canada, and England.

EPIDEMIOLOGY

Eight cases having appendicitis during pregnancy were seen at the Maine Medical Center in this time interval when there were approximately 17,000 births. This incidence is not significantly different from the non-gravid population or that of other reports (Table 1).

Patient ages ranged from 16 to 26 years with a mean of 23 years, which is consistent with other reports.[2,8,10,12,15,17] Since three-quarters of all pregnant women are below the age of 30 years, and three-quarters of all cases of appendicitis are below the age of 30 years, age is of no significance when comparing pregnant with non-pregnant cases with appendicitis.

At the Maine Medical Center, three cases were gravida II and five cases were gravida III. Appendicitis during pregnancy did not appear to be influenced by parity, which is consistent with results seen in other reports.[2,8,10,12,15,17]

Four women developed appendicitis in the first trimester and four in the second trimester at the Maine Medical Center. This is consistent with other series indicating that the second trimester is the more common time during pregnancy for the development of appendicitis (Table 2).

TABLE 1

INCIDENCE
(NUMBER OF CASES PER DELIVERIES)

Babaknia (Baltimore)[2]	1/1500
Mohammed (Canada)[15]	1/1713
Finch (Oxford)[9]	1/1741
Brant (London)[1]	1/1789
Kurtz (N.J.)[12]	1/2055
MMC (Portland)	1/2122
Gomez (Phoenix)[10]	1/2188
Cunningham (Dallas)[8]	1/2700

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TABLE 2

TRIMESTER OF INVOLVEMENT

Thomford (Ohio State)[17]	8—1st,	10—2nd,	4—3rd
Mohammed (Canada)[15]	12—1st,	6—2nd,	2—3rd
Finch (Oxford)[9]	16—1st,	25—2nd,	15—3rd
Cunningham (Dallas)[8]	10—1st,	16—2nd,	8—3rd
Babaknia (Baltimore)[2]	4—1st,	6—2nd,	4—3rd
MMC (Portland)	4—1st,	4—2nd,	o—3rd
	54	67	33

MECHANISM OF APPENDICITIS DURING PREGNANCY

Appendicitis in the first and second trimester is basically the same disease process as that seen in the non-gravid individual; however, as the uterus enlarges it causes the appendix to rotate in a counter clockwise and cephalad direction so that by the fifth month the appendix lies at the iliac crest or the level of the umbilicus. As term approaches, the tip of the appendix comes to lie over the right kidney (Fig. 1). Problems peculiar to appendicitis in pregnancy may include the following: (1) the upward displacement of the appendix out of the pelvis into the general peritoneal cavity where localization of infection is

*From the Department of Surgery, Maine Medical Center, Portland, Maine 04102.

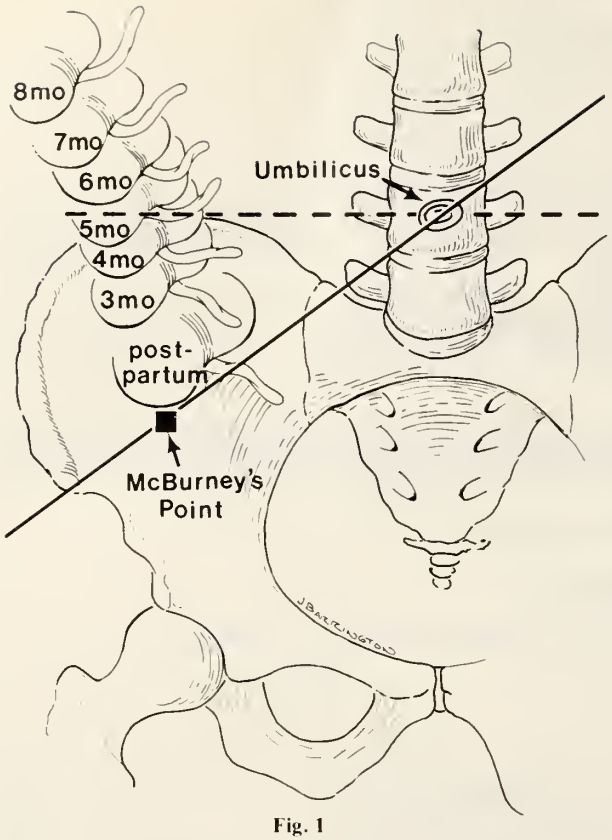


Fig. 1

less likely; (2) the large uterus prevents omentum from localizing an appendiceal abscess, and the uterus itself may become a wall of the abscess with precipitation of premature labor; (3) the general increase in vascularity of the gravid pelvis will allow for an increase in the amount and rate of lymphatic dissemination of infection; (4) the high levels of corticosteroids in pregnancy suppress normal tissue response to inflammation, masking early signs of infection and hindering localization; and (5) Braxton-Hicks contractions also contribute to dissemination of infection by preventing adhesions from forming around the site of inflammation.

Mechanisms of Symptoms

The appendix is embryologically a midline structure so that early pain may be felt in both sides of the abdomen and, like all midgut pain, is centered around the umbilicus. Because the initial pain is due to smooth muscle trying to overcome obstruction, it is colicky in nature but, being mediated by the autonomic nervous system, is dull and diffuse. The onset of colic is followed by nausea and/or vomiting or at least anorexia in association with the edematous distention of the appendiceal peritoneum. At this stage, there may be no change in temperature or pulse rate and tenderness is minimal or absent prior to bacterial proliferation and tissue necrosis. Later, when the inflammed appendix is in contact with the parietal peritoneum of the right iliac fossa, which is supplied by the somatic sensory nerves, pain becomes localized in association with muscle guarding and spasm. In 20% of the cases, the bladder is involved causing dysuria and in 12% inflammation of the rectal wall is responsible for diarrhea.[7]

Presenting Symptoms

Case 1 presented at the Maine Medical Center and did not know that she was pregnant but had had daily vomiting for one week and suddenly developed abdominal discomfort. Case 2 had a known urinary tract infection and presented with nausea, vomiting, and abdominal pain. Case 3 presented with abdominal pain and diarrhea; however, her husband and two children had just recovered from 24 hours of an illness with the same symptoms. Case 4 had presented three months earlier and was thought to have appendicitis and was taken to the operating room where she aborted prior to induction of anesthesia, the appendix remaining intact. She was readmitted with the same symptoms not knowing that she was again pregnant. Case 5 was in and out of the emergency room over a 72-hour period before the correct diagnosis was made. Cases 6, 7, and 8 presented in the typical manner with nausea, vomiting, and right lower quadrant pain. All of the above patients proved to have appendicitis.

Since three-quarters of reported cases of pregnant women have at some time during their pregnancy the symptoms of nausea, vomiting, polyuria, dysuria, and/or abdominal discomfort, all of which may occur with appendicitis, the diagnosis is difficult (Table 3). Reported cases presenting with right upper quadrant pain were in their last trimester. Anorexia, which is thought by some to be pathognomonic of appendicitis, is seen much less when pregnancy is associated with appendicitis.[2]

Physical and Laboratory Findings

Right upper quadrant tenderness was found in the reported patients in the last trimester unless the cecum was bound down in the right iliac fossa. Rebound tenderness and guarding were seen less often in the gravid women with appendicitis because of laxity of the abdominal musculature. Since pregnancy can cause a leukocytosis of up to 15,000, obtaining blood counts and watching for increasing left shift is more reliable[16] (Table 4). The Alder test may differentiate between uterine and extrauterine tenderness. By placing the palpating fingers over the point of maximum tenderness in the right lower quadrant and having the patient turn on the left side, the uterus and adnexa will drop away from the palpating fingers, and if pain is due to adnexa and/or uterine tenderness, it should lessen. However, if due to appendicitis, it should persist.[1]

Differential Diagnosis

A number of cases at the Maine Medical Center had included in the differential diagnosis such processes as urinary tract infections and adnexal pathology. One can usually palpate a tender adnexal mass on pelvic exam but with the ascent of the adnexa out of the pelvis in the last trimester, it becomes impossible to differentiate.[16] A ten minute

Table 3

Presenting Symptoms

	Gomez[10] (Phoenix)	Finch[9] (Oxford)	Cunningham* (Dallas)	Thomford[17] (Ohio State)	Babaknia[2] (Baltimore)	Brant[7] (London)	MMC (Portland)
ABD Pain	100%	100%	100%	100%	100%	100%	100%
RLQ Pain		95%	90%	80%	78%	63%	50%
RUQ Pain		2%	10%	10%	22%		
Anorexia	51%		75%	95%	66%	4%	50%
Nausea	71%		99%	90%		10%	50%
Vomiting	54%		99%	60%		60%	50%
Diarrhea			12%	20%		21%	
Dysuria	10%		25%				

Table 4

Physical Exam

	Thomford[17] (Ohio State)	Mohammed[15] (Canada)	Brant[7] (London)	Finch[9] (Oxford)	Babaknia[2] (Baltimore)	MMC (Portland)
RLQ Tenderness	90%	80%	71%	85%	*	100%
RUQ Tenderness		12%	4%	2%		
Diff ABD Tend	15%		12.5%			
Rebound	75%	100%	54%	55%	70%	50%
Guarding		100%	46%	70%	60%	50%
Fever	20%	60%	50%	15%	18%	60%
WBC 5-10,000	20%	40%			25%	
WBC 10-15,000	75%	50%			50%	25%
WBC 15-20,000	5%	10%			25%	75%
Pulse 100		25%	50%	20%	11%	

*100%—1st, 80%—2nd, 50%—3rd

intravenous pyelogram should be obtained if renal calculi causing obstruction is seriously considered.[14] The round ligament syndrome, which is seen between the 14th and 22nd weeks of pregnancy, involves stretching of the round ligament which, for unknown reasons, is more pronounced on the right than on the left side. Diagnosis is made by palpating the round ligament in the inguinal canal and eliciting the exact pain which may be sharper than that seen in appendicitis and is not usually associated with fever, leukocytosis, nausea and vomiting.[5]

Other processes which must be excluded are: (1) peptic ulcer disease associated with toxemia of pregnancy; (2) volvulus or adhesions when there has been prior surgery; (3) pancreatitis; and (4) salpingitis which is not due to pelvic inflammatory disease but to interference by the growing uterus.[5,14,16]

Operative Factors

Surgeons at the Maine Medical Center used a right paramedian incision in four cases and a muscle splitting incision over the point of maximum tenderness in four cases. If the diagnosis is reasonably certain, a transverse muscle splitting incision over the point of maximum tenderness and elevating the right side of the patient 30 degrees so as to drop the uterus and adnexa away from the operative site provides better access and exposure. If one is not sure of the diagnosis, a right paramedian incision should be considered, allowing access to the uterus and ovaries. Babaknia[2] feels that if one is not sure a transverse muscle cutting incision at the level of the umbilicus should be used for greater exposure to prevent the precipitation of premature labor when retracting the uterus laterally.

None of the patients at the Maine Medical Center suffered from perforation, peritonitis, and/or abscess formation and did not require drains or antibiotics. Reported experience noted that the indications for drainage and antibiotics are not altered by the pressure of pregnancy.[2]

Spinal anesthesia was used in four cases and general anesthesia using halothane was used in the remaining four. None suffered postoperative complications from their anesthesia. Two forms of accepted anesthesia are spinal anesthesia which can block the sympathetic tone of the uterus and potentially cause under-perfusion of the uterus and halothane anesthesia which is considered to be better as it is able to relax the uterus without causing hypoperfusion in therapeutic ranges and decreases the chance of precipitating labor when the uterus is retracted.[18]

Obstetrical Management

Since none of the cases at the Maine Medical Center were in their last trimester or had associated peritonitis and/or perforation, C-section was not considered. There was no maternal and/or fetal morbidity or mortality. Five of the eight women went on to have normal full term vaginal deliveries, the other three being lost to follow-up. This compares with

similar data in other reports.[17] Since almost 100% of gravid females who develop peritonitis in the last trimester will develop premature labor within 24 to 48 hours and have an associated high fetal wastage, Babaknia feels that C-sections should be performed when generalized peritonitis occurs in the last trimester. If labor is already in progress, an appendectomy should be performed after vaginal delivery; however, if the patient is in early labor and there is no contraindication, C-section should be done. Some reports recommend that in addition to C-sections hysterectomy be considered if, along with peritonitis, there is perforation and/or abscess formation.[2]

In 1908, a 25% maternal mortality and a 40% fetal mortality was reported; however, in 1976 only a 0.01% maternal mortality and an 8.5% fetal mortality was reported, usually only occurring with perforation and generalized peritonitis.[2] Late morbidity following perforated appendicitis leading to peritoneal adhesions may include sterility secondary to tubal involvement.

Summary

Experience at the Maine Medical Center over a recent ten-year period with eight cases with appendicitis during pregnancy was comparable with series reported elsewhere. It is generally agreed that the surgeon should not procrastinate in this potentially devastating syndrome. Early operation and an error in diagnosis carries much less morbidity than delaying for fear of inducing abortion. Surgery should not be withheld if there is a question of appendicitis during pregnancy.

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Brief Summary

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Product Information as of September, 1977

U.S. Patent 2,985,558

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Recent Developments in Coronary Artery Surgery in Maine

JEREMY R. MORTON, M.D.*

Since January 1978, 400 coronary artery bypass procedures have been performed at the Maine Medical Center with three deaths. The purpose of this paper is to describe the changing picture of myocardial revascularization at the Maine Medical Center including early results, late survival, and a look at economics. Although the fundamentals of the coronary bypass procedure have changed very little in the past ten years, refinements in technique have reduced the mortality and morbidity of the operation.

Nine hundred and eighty-five coronary bypass procedures were performed by six surgeons† at the Maine Medical Center from 1972 to October 1, 1978, distributed chronologically as illustrated in Table 1. The mean age of these patients is 55 years and ranges from 22 to 76 years. The number of bypass grafts performed per patient during 1975 and 1977 is shown in Table 2. Experience here as elsewhere suggests that the incidence of recurrent angina after surgery is less when all of the significantly obstructed coronary vessels, including major branches, are bypassed. Accordingly the number of bypass grafts per patient has increased.

TABLE 1

NUMBER OF CORONARY BYPASS CASES BY YEAR

Year	*No. of Cases*
1972	3
1973	57
1974	127
1975	139
1976	212
1977	246
1978 (Oct. 1)	201
TOTAL	985

TABLE 2

NUMBER OF VESSELS BYPASSED

No. of Grafts	*1975 Percent*	*1977 Percent*
1	14	7
2	40	30.5
3	32	44
4	14	17
5	0	1.5
TOTAL	100	TOTAL 100

TABLE 3

EARLY MORTALITY
UNCOMPLICATED CORONARY DISEASE

Time Interval	*No. of Deaths*	*Percent*
1972-1976	8	1.6%
1977	4	1.6%
1978 (Oct. 1)	2	1.0%

TABLE 4

POSTOPERATIVE MYOCARDIAL ENZYMES BEFORE AND AFTER USE OF POTASSIUM ARREST TECHNIQUE

	Local Hypothermia	*Local Hypothermia Potassium Arrest*
Significant Elevation (CPK > 300 U and M.B. Fraction > 7%)	13.1%	6.2%
CPK and LDH Elevation with LDH Inversion	6.6%	2.5%
Absolute Value of CPK M.B. Fraction (Mean)	28.4U	17.3U

OPERATIVE MORTALITY

The operative mortality in patients undergoing straightforward coronary bypass surgery remained stable at 1.6% during the six-year period prior to 1978 (Table 3). Improved techniques were offset by more extensive disease in the operated patients. During the past 18 months, however, in response to a new technique providing improved intraoperative myocardial preservation, the operative mortality has been reduced to less than 1% as noted above.

POTASSIUM ARREST

In order to provide a dry and quiet field in which to construct the tiny distal vein-to-coronary anastomoses, it is necessary to interrupt the coronary blood flow by cross-clamping the ascending aorta and cooling the heart locally. Before 1977, this was done intermittently and after each anastomosis the clamp was released and the heart allowed to recover for a ten minute period before being reclamped and recooled for the next graft. The technique was designed to subject the myocardium to the shortest period of continuous ischemia. Approximately 80% of the patients, however, required temporary blood pressure support with an inotropic agent such as, Dopamine, immediately after coming off cardio-

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Table 5

Mortality in Combined Procedures

Year	*Cases*	*Deaths*	*Percent Mortality*
1974	10	2	20%
1975	15	3	20%
1976	20	5	25%
1977	15	1	6.6%
1978 (Oct. 1)	19	1	5.2%

pulmonary bypass. Additionally 30% of the patients exhibited significantly elevated enzymes postoperatively and in 10% there was electrocardiographic evidence of myocardial injury.

Two years ago, the technique of potassium arrest was introduced in which the heart is abruptly arrested by rapidly infusing a chilled electrolyte solution containing 25 meq/L of KCl into the aortic root between the clamp and the aortic valve. The heart is simultaneously submerged in ice cold saline and is thus maintained in a state of continuous cold arrest until all of the distal anastomoses and whatever valve or aneurysm surgery is required has been completed. Using this method the heart appears to be more resilient than before even when bypass extends beyond two hours. Less than 10% of patients now require inotropic support and many fewer patients show significant elevation of postoperative enzymes (Table 4). In patients undergoing more extensive operations involving procedures such as, valve replacement or ventricular aneurysm resection in combination with coronary bypass grafting, the reduction in mortality associated with the potassium arrest technique is much more impressive. During the period from 1974-1977, the mortality for this group remained quite constant at 20-25% (Table 5). With the introduction of potassium arrest, however, this figure dropped abruptly to approximately 6% where it has remained.

Clinical Results

With the help of our referring physicians, we have been able to accumulate current follow-up information on 94% of the operated patients. The results are illustrated in Table 6. Approximately 80% of the patients have remained entirely symptom free. Of the remainder most have only mild angina with heavy exertion and lead normal lives. Six percent have developed moderate recurrent angina but are nonetheless improved over their preoperative status. Two percent are no better.

It is encouraging to note that relatively few patients, who were asymptomatic at one year, have subsequently developed recurrent symptoms.

Table 6

Clinical Results

Year of Surgery	*No. of Pts.*	*Current Status*			
		Asymptomatic	*Mild Angina**	*Mod. Angina*	*Severe Angina*
1972-73	42	76%	17%	4%	3%
1974	109	74%	17%	7%	2%
1975	118	80%	11%	7%	2%
1976	164	79%	15%	5%	1%
1977	261	81%	13%	5%	1%

*Able to work or lead a normal life.

Late Mortality

The effectiveness of coronary bypass surgery in relieving angina is now well established. Longterm survival, however, continues to be the subject of much debate. In our series, 26 patients have died later than 30 days after surgery (Table 7). Nine patients have succumbed to noncardiac causes while 17 have died of either cardiac or unknown causes. A more meaningful figure is the late mortality expressed as a percent of patients at risk over a given period of time or percent per patient year at risk. These numbers are shown in Table 8. The yearly attrition rate is remarkably constant and averages 0.6%. The cumulative mortality combines early and

Table 7

Late Mortality

Cause	*Number of Patients*
Cardiac	9
Unknown	8
	17
Non-Cardiac	9
TOTAL	26

Table 8

Late Mortality

Interval Since Surgery	*No. of Patients*	*Percent per Patient Year at Risk*
Less Than 1 Year	4	0.4%
1-2 Years	8	1.0%
2-3 Years	3	0.6%
3-4 Years	2	0.6%
4-5 Years	1	0.6%
	Average Per Year: 0.64%	

Table 9

Cumulative Mortality	
Early Mortality	1.6%
Late Mortality Per Year	0.64%
Cumulative Surgical Mortality:	
3 Years	3.5%
5 Years	4.8%

Table 10

Economic Results	
Patients Followed Beyond 1 Year	579
Patients Returned to Work	320 (55%)
Total Cost of Surgery	$5,200,000
Patient Working Years to Date	718
Gross Patient Product	$10,770,000

late mortality as illustrated in Table 9. Accordingly if a patient with significant coronary disease is treated surgically, his chances of surviving three years (including noncardiac causes of death) is 95.4% and five years is 93.4%. This approximates five-year survival in the normal population adjusted for age and sex distribution which is 92.7%.[1]

These survival figures are substantially better than those of any medically treated series of similar composition.[2,3,4] Murphy, et al[2] in their widely publicized VA study reported on a medically treated group in which left main and unstable angina patients had been selected out and still their three-year survival was only 86%. Bruschke, et al[3] reported a series of 590 angiographically matched medically treated patients in which the five-year survival was 65.4%.

Economic Considerations

With the current national emphasis on the cost of medical care, some have criticized that the economy cannot afford the growing number of coronary operations. Nearly all of the patients, who are candidates for surgery, are disabled by their disease and must be supported by the Government or insurance companies. On the other hand, 55% of those operated on in this series have returned to work and are currently supporting the economy. Most of the remainder are either retired or cannot find employment. Table 10 shows the total cost of surgery for all of the patients being followed who are more than one year since their surgery. If one assigns a figure of $15,000 per year to each patient who has returned to work, representing the difference between his earnings and the cost of supporting him were he disabled, the total "gross patient product" would come to more than twice the cost of the surgery for the entire group. This benefit to cost ratio should continue to increase each year as these patients accumulate more postoperative work years.

Conclusion

Recent refinements in intraoperative myocardial preservation have reduced the 30-day mortality of bypass surgery at the Maine Medical Center to less than 1% with a yearly attrition of 0.6%. Surgery provides both relief of angina and extension of life.

Looked at from an economic standpoint, coronary surgery more than pays its way.

Acknowledgment

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Combination Chemotherapy of Advanced, Diffuse, Non-Hodgkin's Lymphoma: Results with Cyclo-phosphamide, Adriamycin, Vincristine, Prednisone, and Bleomycin (CHOP-Bleo)

Delvyn C. Case, Jr., M.D., F.A.C.P.*

The histologic classification of the non-Hodgkin's lymphomas described by Rappaport defines several distinct groups with clinically significant differences in natural history and response to therapy.[1] This classification emphasizes the significance of a nodular growth pattern which predicts, even for advanced stages, a relatively indolent cause and a susceptibility to treatment with relatively moderate chemotherapy programs.[2] In contrast, a diffuse growth pattern among the poorly differentiated lymphomas predicts more aggressive disease.[3] These lymphomas, including diffuse poorly-differentiated lymphocytic (DPDL), diffuse histiocytic (DHL), and diffuse mixed histiocytic—lymphocytic (DMH-L) subtypes, have proved more resistant to conventional treatment and have a relatively poor prognosis.[4] Staging studies of non-Hodgkin's lymphomas have indicated that the majority of diffuse poorly differentiated lymphocytic and histiocytic lymphomas are advanced at diagnosis requiring reliance upon chemotherapy.

Several studies have shown that combination chemotherapy is superior to single-agent therapy in the management of advanced non-Hodgkin's lymphoma.[5-7] The three-drug regimen, cyclophosphamide, vincristine (Oncovin®), and prednisone (COP) has been shown to produce complete remissions in 77% of patients with nodular histology. While transient partial remissions are frequent in patients with diffuse histology, only 14% of such patients achieve a complete remission (CR) and long-term survival.[8] The addition of bleomycin and hydroxyldaunorubicin or doxorubicin (Adriamycin) both active in the non-Hodgkin's lymphomas[9-12] has significantly increased the complete response rate in the diffuse poorly-differentiated lymphocytic, histiocytic, and mixed groups.[13-14]

The rationale for combining five agents is based upon qualitatively different mechanisms of action and toxicity, exploitation of cell cycle kinetics, and experimental evidence of synergism for Adriamycin and cyclophosphamide.[15-16]

This report presents the results of the CHOP-Bleo program (**c**yclophosphamide, **h**ydroxyldaunorubicin (Adriamycin), vincristine (**O**ncovin), **p**rednisone, and **bleo**mycin) in patients with advanced diffuse unfavorable lymphomas.

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Table 1

Histopathologic Classification	
Diffuse poorly-differentiated lymphocytic (DPDL)	7
Diffuse mixed lymphocytic-histiocytic (DML-H)	1
Diffuse histiocytic (DHL)	9
	17

Materials and Methods

From July 1, 1976 to December 1, 1977, 17 previously untreated patients with diffuse non-Hodgkin's lymphoma with unfavorable histologies were entered on the CHOP-Bleo protocol. All patients were evaluable; and no patient was excluded from analysis because of early death.

All pathologic sections were classified according to the histologic criteria of Rappaport.[17] The various histologic groups represented and treated in this study are indicated in Table 1.

Clinical staging included complete blood count with platelet count, chest x-ray, SMA, intravenous pyelogram, liver and spleen scan, bone survey and bone scan in symptomatic patients, bone marrow aspiration and biopsy, and percutaneous liver biopsy if liver involvement was suspected. Bilateral pedal lymphangeography was performed in patients who did not have superior vena cava syndrome or massive abdominal adenopathy which might result in complications. In the latter circumstances, abdominal sonogram and/or C.T. scan were employed to define retroperitoneal disease. Routine staging laparotomy was not carried out. The extent of disease was categorized according to the Ann Arbor staging classification.[18]

The clinical characteristics of the 17 patients are presented in Table 2. Four patients with DHL had Stage III disease while 5 had Stage IV disease. Patients with DHL with Stage IV disease had varied extranodal involvement: bone marrow (1), effusions with pleural seeding (2), skin (1), and gastrointestinal (1). Two of the 7 patients with DPDL had Stage III disease. All 5 with Stage IV disease had bone marrow involvement.

TABLE 2

CLINICAL CHARACTERISTICS OF PATIENTS

Age	
Median	58
Range	19-76
Male/female	10/7
Prior therapy	0
Stage III	7
Stage IV	10
Bone marrow	6
Effusions (with pleural seeding)	2
Skin	1
Gastrointestinal	1

Combination chemotherapy with the CHOP-Bleo program consisted of 12 monthly cycles of therapy (Figure 1). Adriamycin was discontinued when the total cumulative dose reached 450 /m.^{2} (9 cycles). Bleomycin was continued for the 12 full cycles (total dose 192 units/m.^{2}). Methotrexate (6.25 mg./m.^{2}) was given intrathecally every 2 months during therapy to those patients who had bone marrow involvement. All treatment was able to be given in the office on an outpatient basis.

Blood counts were obtained before each cycle. Doses of Adriamycin and cyclophosphamide were reduced according to the following schedule: white blood count (WBC) 2000-3500/mm.^{3} or platelets 50,000-100,000/mm.,^{3} 50% decrease; WBC under 2000/mm.^{3} or platelets under 50,000/mm.,^{3} dosage delayed. Vincristine was reduced by 50% if moderate neuropathy developed and discontinued with severe neuropathy.

Prednisone was reduced or withheld if severe side effects were encountered. Bleomycin and Adriamycin were reduced if there were any signs of cardiopulmonary toxicity.

Complete remission (CR) was defined as complete disappearance of all measurable disease persisting for a minimum of one month. All procedures involved in initially defining the extent of disease were repeated short of laparotomy and laparoscopy to confirm complete remission. Patients who had a greater than 50% reduction of measurable disease which lasted for a minimum of one month were considered to have a partial remission (PR).

RESULTS

Response

The objective response rate in this report was 94% (Table 3). All responders were complete responders. The median time from start of therapy to complete remission was 8 weeks. Time to achieve CR did not significantly differ among the 3 histologic groups. Only one patient failed therapy.

There were 2 drug deaths. These patients died at 2 and 3 months. Both patients were in remission. Of the other 14 patients in CR, 11 are still in remission

FIGURE 1

CHEMOTHERAPY TREATMENT PLAN (CHOP-BLEO)

Cyclophosphamide	750 mg./m^2, I.V. day 1
Hydroxyldaunorubicin (Adriamycin)	50 mg./m^2, I.V. day 1
Vincristine (**O**ncovin)	1.4 mg./m^2, I.V. days 1 & 8
Prednisone	100 mg. P.O. days 1-5
Bleomycin	8 units/m^2, I.V. days 1 & 8

Treatment every 28 days for total of 12 cycles

TABLE 3

RESULTS (CHOP-BLEO)

	Number of Patients	*Complete Responses*
DPDL	7	7 (100%)
DMH-L	1	1 (100%)
DHL	9	8 (89%)
	17	16 (94%)

from 13+ to 31+ months (13+, 18+, 19+, 19+, 19+, 21+, 30+, 30+, 30+, 30+, 31+) (Median 19+ months). Three patients have relapsed: one patient with DHL had extensive abdominal disease and relapsed at 11 months; two patients with DPDL and bone marrow involvement relapsed at 9 and 12 months. None of the patients in remission for 13 months or longer has relapsed.

Dose Adjustment and Toxicity

The doses of cyclosphosphamide and Adriamycin were adjusted in 25% of patients owing to myelosuppression. Leukopenia was more common than thrombocytopenia. Counts were not routinely checked during each cycle unless patients were symptomatic. On this program, pretreatment counts on the day of therapy were satisfactory to protect against undue myelosuppression.

Therapy was well-tolerated. Half the patients required deduction of the dosage of vincristine because of peripheral neuropathy. This toxicity was especially seen in the older patients. High fever from bleomycin necessitated the discontinuation of this drug in one patient. Pulmonary toxicity was not seen in any patient. Total dose of bleomycin used in this program was 192 units/m.^{2} over a 12-month period. Total alopecia was observed in all patients but was reversible. No cardiac toxicity was observed. (Dose of Adriamycin limited to 450 mg./m.^{2}).

While the treatment program was well-tolerated in most patients, 2 patients early in the program (at 2 and 3 months) expired from fatal bacterial infection during drug-induced pancytopenia. None of the other patients required hospitalization during treatment. No opportunistic infections occurred.

Relapse Patterns and Central Nervous System Involvement (CNS)

Of the 17 patients treated with the CHOP-Bleo

program, 3 have relapsed. One patient with DHL presented with widespread abdominal disease and relapsed in the abdomen after 11 months in CR. He expired 3 months later from refractory disease. Two patients with DPDL (ages 19 and 25) have relapsed. Both patients had widespread bone marrow disease at the onset of therapy. Both patients relapsed in the CNS (despire prophylactic methotrexate) followed by bone marrow relapse. Both patients rapidly progressed and died within 2 months after relapse.

Discussion

A high complete remission rate in patients with diffuse lymphomas of unfavorable histologies has been achieved with the CHOP-Bleo program. Employing cyclophosphamide, vincristine, and prednisone (COP), CR rates from 14%-35% have been achieved in the diffuse histologies.[5-8,19-20] The addition of Adriamycin or bleomycin improves the CR rate from 43 to 64%.[21,22] Results of a 5-drug regimen combining all the drugs mentioned has previously shown a CR rate of 66%.[13] In the CHOP-Bleo program using a different schedule of drug administration and timing, a 94% CR rate in a small series has been achieved. Importantly, only 3 of 16 patients (18%) have relapsed with remissions now lasting 13+ to 31+ months. No patient with a remission lasting longer than 13 months has relapsed. Since the median survival of DHL and DPDL is 1 and 2 years respectively,[4] significant survival gains for patients with these diseases will be obtained with this program.

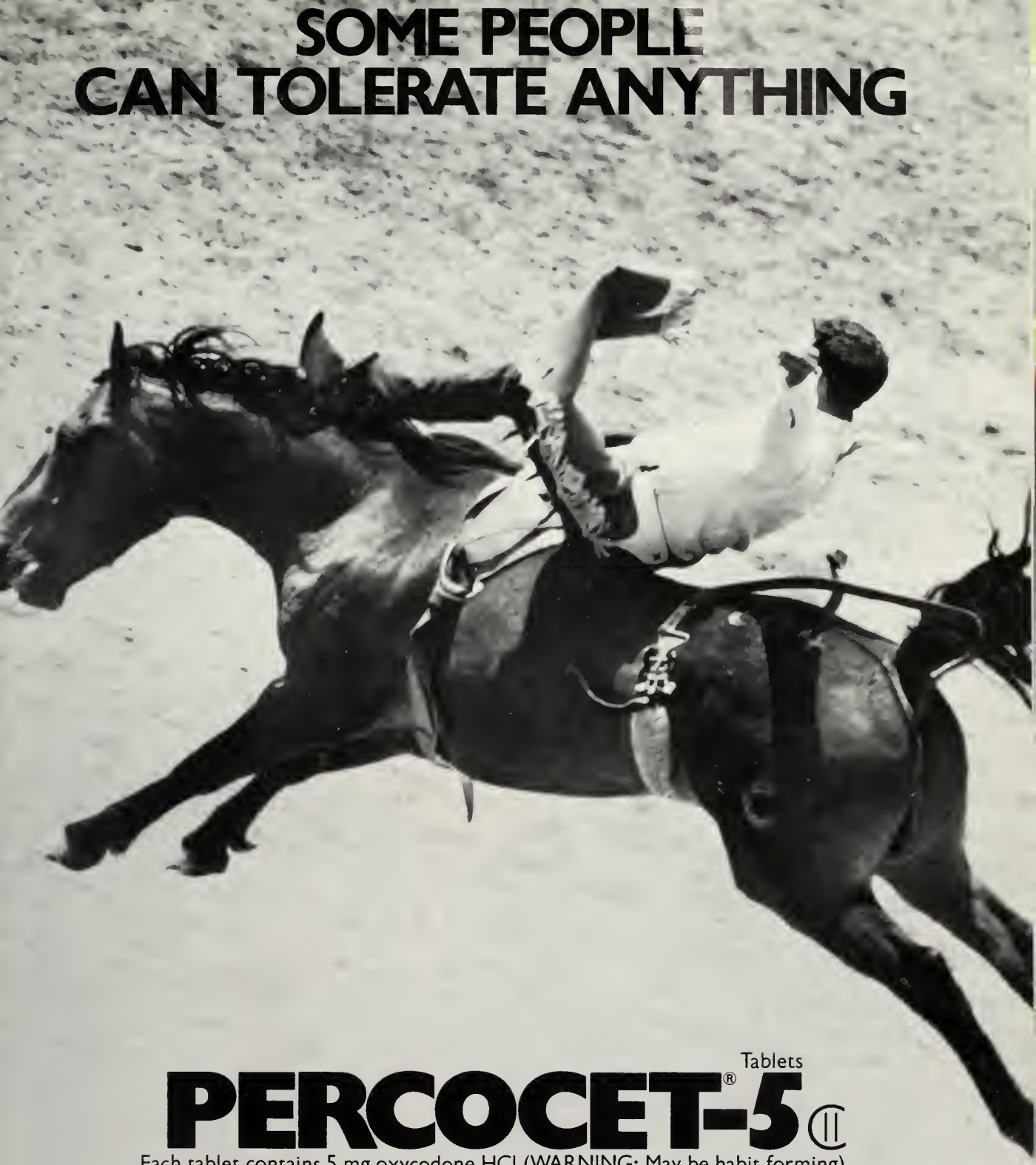
CNS involvement occurred in 2 (18%) of the patients in this group. Both of these patients had DPDL and relapsed initially in the CNS, followed by bone marrow relapse. While cell surface marker studies were not done, the clinical courses suggested that these patients may have had a T-cell disorder and might have benefited from a more prolonged leukemia program. These two patients both received prophylactic intrathecal methotrexate. Two-thirds of the other patients with bone marrow involvement have not shown any signs of CNS relapse. Bone marrow involvement is the important factor in predicting CNS relapse.[23] The relapse rate in this series is one- half that seen in another that did not include CNS prophylaxis.[13]

Intensive treatment of the diffuse non-Hodgkin's lymphoma with the CHOP-Bleo program produces a high response rate with long remissions expected. The prolonged treatment program with the doses of Adriamycin and bleomycin spread out over one year may account for the low relapse and complication rate related to these drugs. CNS prophylaxis is indicated in patients with bone marrow involvement as it reduces the relapse rate and failure rate in the CNS. Methotrexate alone has been shown useful in this study. Radiation therapy, high-dose methotrexate with citrovorum rescue, or dexamethasone (substituted for prednisone), may be other alternatives.[24] Modifications of this program based upon further

Continued on Page 352

Tablets
PERCOCET®-5 (II)
Brief Summary of Prescribing Information
DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).
INDICATIONS For the relief of moderate to moderately severe pain.
CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.
WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.
Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.
Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.
Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.
Usage in children PERCOCET®-5 should not be administered to children.
PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.
Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.
Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.
ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.
Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.
DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.
DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS
DEA Order Form Required.
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SOME PEOPLE CAN TOLERATE ANYTHING



Tablets

PERCOCET®-5 (II)

Each tablet contains 5 mg oxycodone HCl (WARNING: May be habit forming) and 325 mg acetaminophen (APAP)

FOR THOSE WHO CAN'T TOLERATE ASPIRIN

indicated for moderate to moderately severe pain

contains well-tolerated acetaminophen

provides the effective analgesia of oxycodone

- ☐ scored tablet permits finer titration
- ☐ convenient, economical q6h dosage

Please see opposite page for brief summary of prescribing information.

follow up of these patients should allow for rational development of program to produce cures in patients with diffuse non-Hodgkin's lymphoma.

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Continued on Page 368

- Bendectin continues to be the only product indicated exclusively for morning sickness — nothing else.
- Convenient bedtime dosage.
- Works in the morning when she needs it most.

Bendectin®

AVAILABLE ONLY ON PRESCRIPTION

Brief Summary

INDICATION
Nausea and vomiting of pregnancy.

PRECAUTIONS
Because of potential drowsiness, Bendectin should be prescribed with caution for patients who must drive automobiles or operate machinery.
Studies in rats and rabbits have revealed no suggestion of drug-induced fetal abnormalities at doses of Bendectin up to 90 times the maximum human dose. In addition, several epidemiologic studies in women who received Bendectin during pregnancy have shown that the incidence of birth defects in their offspring is no higher than in women not taking the drug during pregnancy. Nevertheless, like all drugs considered for use during pregnancy, particularly during the first trimester, Bendectin should be used only when clearly needed.

ADVERSE REACTIONS
The adverse reactions that may occur are those of the individual ingredients. Doxylamine succinate may cause drowsiness, vertigo, nervousness, epigastric pain, headache, palpitation, diarrhea, disorientation, or irritability.
Pyridoxine hydrochloride is a vitamin that is generally recognized as having no adverse effects.

DOSAGE AND ADMINISTRATION
2 Bendectin tablets at bedtime. In severe cases or when nausea occurs during the day: 1 additional Bendectin tablet in the morning and another in midafternoon.

Product Information as of January, 1978

References:
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2. Data on file, MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215

Merrell

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1830: A decoction of columbo root and peppermint 3 or 4 times a day should be taken for the sickness to which pregnant females are commonly subject.[1]

TODAY: Clinical studies show statistically proven efficacy for morning sickness of pregnancy with delayed-release Bendectin tablets.[2]



In morning sickness confidence begins with

Bendectin®

Each tablet contains doxylamine succinate 10 mg., pyridoxine hydrochloride 10 mg.

trusted alternative to nausea and vomiting of pregnancy

For prescribing information see opposite page.



A reminder

ZYLOPRIM®
(allopurinol)

100 and 300 mg scored Tablets

- inhibits uric acid formation
- helps prevent urate crystal depositions in synovia
- reduces risk of uric acid lithiasis

INDICATIONS AND USE: This is not an innocuous drug and strict attention should be given to the indications for its use. Pending further investigation, its use in other hyperuricemic states is not indicated at this time.

Zyloprim® (allopurinol) is intended for:

1. treatment of gout, either primary, or secondary to the hyperuricemia associated with blood dyscrasias and their therapy;
2. treatment of primary or secondary uric acid nephropathy, with or without accompanying symptoms of gout;
3. treatment of patients with recurrent uric acid stone formation;
4. prophylactic treatment to prevent tissue urate deposition, renal calculi, or uric acid nephropathy in patients with leukemias, lymphomas and malignancies who are receiving cancer chemotherapy with its resultant elevating effect on serum uric acid levels.

CONTRAINDICATIONS: Use in children with the exception of those with hyperuricemia secondary to malignancy. The drug should not be employed in nursing mothers.

Patients who have developed a severe reaction to Zyloprim should not be restarted on the drug.

WARNINGS: ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme) and very rarely a generalized vasculitis which may lead to irreversible hepatotoxicity and death.

A few cases of reversible clinical hepatotoxicity have been noted and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. Accordingly, periodic liver function tests should be performed during the early stages of therapy particularly in patients with pre-existing liver disease.

Patients should be alerted to the need for due precautions when engaging in activities where alertness is mandatory.

Nevertheless, iron salts should not be given simultaneously with Zyloprim. This drug should not be administered to immediate relatives of patients with idiopathic hemochromatosis.

In patients receiving Purinethol® (mercaptopurine) or Imuran® (azathioprine), the concomitant administration of 300-600 mg of Zyloprim per day will require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of Purinethol or Imuran should be made on the basis of therapeutic response and any toxic effects.

Usage in Pregnancy and Women of Childbearing Age Zyloprim® (allopurinol) should be used in pregnant women or women of childbearing age only if the potential benefits to the patient are weighed against the possible risk to the fetus.

PRECAUTIONS: Some investigators have reported an increase in acute attacks of gout during the early stages of allopurinol administration, even when normal or subnormal serum uric acid levels have been attained.

It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. This interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

A fluid intake sufficient to yield a daily urinary output of at least 2 liters and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable to (1) avoid the theoretic possibility of formation of xanthine calculi under the influence of Zyloprim therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Patients with impaired renal function require less drug and should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in renal function appear.

In patients with severely impaired renal function, or decreased urate clearance, the half-life of oxipurinol in the plasma is greatly prolonged. Therefore, a dose of 100 mg per day or 300 mg twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels. Such patients should be treated with the lowest effective dose, in order to minimize side effects.

Mild reticulocytosis has appeared in some patients.

As with all new agents, periodic determination of liver and kidney function and complete blood counts should be performed especially during the first few months of therapy.

ADVERSE REACTIONS:

Dermatologic: Because in some instances skin rash has been followed by severe hypersensitivity reactions, it is recommended that therapy be discontinued at the first sign of rash or other adverse reaction (see WARNINGS). Skin rash, usually maculopapular, is the adverse reaction most commonly reported.
Exfoliative, urticarial and purpuric lesions, Stevens-Johnson syndrome (erythema multiforme) and toxic epidermal necrolysis have also been reported.
A few cases of alopecia with and without accompanying dermatitis have been reported.
In some patients with a rash, restarting Zyloprim (allopurinol) therapy at lower doses has been accomplished without untoward incident.

Gastrointestinal: Nausea, vomiting, diarrhea, and intermittent abdominal pain have been reported.

Vascular There have been rare instances of a generalized hypersensitivity vasculitis or necrotizing angiitis which have led to irreversible hepatotoxicity and death.

Hematopoietic Agranulocytosis, anemia, aplastic anemia, bone marrow depression, leukopenia, pancytopenia and thrombocytopenia have been reported in patients, most of whom received concomitant drugs with potential for causing these reactions. Zyloprim® (allopurinol) has been neither implicated nor excluded as a cause of these reactions.

Neurologic. There have been a few reports of peripheral neuritis occurring while patients were taking Zyloprim. Drowsiness has also been reported in a few patients.

Ophthalmic: There have been a few reports of cataracts found in patients receiving Zyloprim. It is not known if the cataracts predated the Zyloprim therapy. "Toxic" cataracts were reported in one patient who also received an anti-inflammatory agent, again, the time of onset is unknown. In a group of patients followed by Gutman and Yü for up to five years on Zyloprim therapy, no evidence of ophthalmologic effect attributable to Zyloprim was reported.

Drug Idiosyncrasy Symptoms suggestive of drug idiosyncrasy have been reported in a few patients. This was characterized by fever, chills, leukopenia or leukocytosis, eosinophilia, arthralgias, skin rash, pruritus, nausea and vomiting.

OVERDOSAGE: Massive overdosing, or acute poisoning, by Zyloprim has not been reported.

HOW SUPPLIED: 100 mg (white) scored tablets, bottles of 100 and 1000; 300 mg (peach) scored tablets, bottles of 30, 100 and 500. Unit dose packs for each strength also available.

Complete information available from your local B. W. Co. Representative or from Professional Services Department PML.

U.S. Patent No. 3,624,205 (Use Patent)

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Survey of Office Visits to Selected Family Physicians in Southern Maine

J. Michael Taylor, M.D., M.P.H.* and Walter John Murrell**

Introduction

In order to develop a more meaningful program for continuing medical education for Family Physicians, patient characteristics were documented in the offices of eleven practicing physicians for one week during July 1978. By using a slightly modified version of the patient encounter form developed by the National Ambulatory Care Survey, it was possible for us to also compare these eleven practices with national data. The patient encounter form can be seen in Figure 1.

Hospitals in Maine and throughout the United States have long gathered information describing demographic, illness, and treatment characteristics of patients admitted and discharged. This information has been used not only for planning, for characterizing, and for financing, but also for both evaluation and continuing education. However, except for the National Ambulatory Care Survey,[1] little information exists which describes patients seen in the offices of family physicians. For purposes of documenting educational experience, family practice residencies in Maine and throughout the United States gather information about the patient encounters in the family practice units. Family practice units differ in many ways from private practices, however.

Methodology

During the summer of 1978, the junior author, a student at Tufts University School of Medicine, elected to survey selected practices. Using the active staff roster of the Department of Family Medicine at the Maine Medical Center, 17 physicians were contacted about participating in the survey. A requirement for participation was that the survey would be completed during either the first or second week of July. Eleven of the 17 practicing family physicians agreed to participate and formed the core of the analysis. Simultaneous with the one week patient encounter data collection by the eleven practices, the encounters at the Family Practice Unit of the Department of Family Medicine were also tabulated. The encounters of the Family Practice Unit, which numbered 204 during that week, are excluded from this analysis since the Model Family Practice Unit is primarily an educational unit and different from a private practice. Each of the eleven practices was asked to describe each patient office encounter during either the first or second week in July 1978. This 100% sample in each practice excluded phone calls, house calls, and hospital visits.

Two modifications were made in the National Ambulatory Medical Care Survey form displayed in Figure 1. Question #4 concerning color or race was not included and question #12, meant to gather information on the duration of visit, was also not included. Based on interpretation of published data,[2] the question of self reported time was considered to be unreliable. Also the patient record was converted from an individual encounter form as indicated in Figure 1 to log paper so that the office staff could compile several patients (up to 20 on a single sheet). Generally, the office staff completed all of the items except for question #9, the Physician's Principle Diagnosis, and question #10, the Treatment or Service that was provided. These questions were completed by the physician who provided the care.

Findings

Eight hundred and fifty-six visits were made to the eleven practices during the sample period. The number of visits per practice ranged from 50 to 115. No documentation was made concerning the numbers of hours that each practice was open during the sample period.

The age distribution of the patients making these visits are tabulated in Table 1. Southern Maine practices had a higher proportion of patients in the 6-24 age grouping and lower proportion in the 25-64 age grouping than the National Survey. This difference in patient age distribution cannot be explained by differences in population age distribution.

It must be noted here that aggregating patient-described symptoms into categories is judgmental since patients, in their own words, describe symptoms. Table 2 lists the twenty most common problems or symptoms of the eleven practices. A ranked comparison with the National data is given in Table 3. It is interesting to note that some symptom categories from the National Survey data are not among the top twenty from the Maine practices: specifically, visits for medication, weight gain, vertigo, and fever.

Prior visit status in the Maine practices show the 25.4% of the patients were seen for the first time. This is considerably higher than the 12.2% found in the National Survey and could relate to the time of sampling, July, when southern Maine has many visitors (Table 4). There may be other explanations.

Table 5 shows the major reason for visits in the eleven practices. Comparison data are not available from the National Survey. In decreasing frequency, the reasons are: 1) acute problem; 2) chronic problem

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FIGURE 1

NATIONAL AMBULATORY MEDICAL CARE SURVEY

Patient Record

1) Date of Visit

2) Date of Birth

3) Sex

4) Color or Race

5) Patient's Principle Problem Complaint or Symptom(s)

(in patient's own words)

5a) Most Important

5b) Other

6) Seriousness of Problem in Item 5a

Very Serious
Serious
Slightly Serious
Not Serious

7) Have You Ever Seen This Patient Before?

If yes, for the problem indicated in item 5a?

8) Major Reason For This Visit

A) Acute Problem
B) Acute Problem, Follow-Up
C) Chronic Problem, Routine
D) Chronic Problem, Flare-Up
E) Prenatal Care
F) Postnatal Care
G) Postoperative Care
H) Well Adult/Child Exam
I) Family Planning
J) Counseling/Advice
K) Immunization
L) Referred by other Physician/Agency
M) Administrative Purpose
N) Other

9) Physician's Principle Diagnosis This Visit

10) Treatment/Service Ordered or Provided This Visit

A) None Ordered/Provided
B) General History/Exam
C) Lab Procedure/Test
D) X-Rays
E) Injection/Immunization
F) Office Surgical Treatment
G) Prescription Drug
H) Non-Prescription Drug
I) Psychotherapy/Therapeutic Listening
J) Medical Counseling/Advice
K) Other

11) Disposition This Visit

A) No Follow-Up Planned
B) Return At Specific Time
C) Return If Needed, P.R.N.
D) Telephone Follow-Up Planned
E) Referred to Other Physician/Agency
F) Returned to Referring Physician
G) Admit to Hospital
H) Other

12) Duration Of This Visit

follow-up; 3) acute problem follow-up; 4) well child or well adult exam; 5) chronic problem flare-up; and 6) prenatal care. The 15 most frequent diagnoses are noted in Table 6. A comparison is not made with the National Survey because of the absence of a uniform method of coding the diagnosis. For example, upper respiratory infection and acute pharyngitis were called bacterial infection under our coding scheme but were separated in the National Survey. It is worthwhile noting, however, that a comparison of the diagnoses reveals that surgical aftercare and obesity which were #4 and #6 in frequency in the National data are not in the top 15 diagnoses from the eleven practices. Treatments or services ordered or provided at the encounter are found in Table 7. In the eleven Maine family practices, an encounter was more likely to result in a general history/examination, medical counselling/advice, and laboratory procedure/test. However, Maine family physicians seem less likely to order or provide injection/immunization and both prescription and non-prescription drugs. It should be noted that these columns can sum greater than 100% because more than one treatment or service can be ordered for each encounter.

TABLE 1

AGE DISTRIBUTION OF ENCOUNTERS

	National Survey	*Maine Family Practices*
TOTAL NUMBER OF PATIENTS:	263,390	856
AGE:		
0-5	16.4%	10.0%
6-15	16.3%	12.6%
16-24		18.5%
25-44	24.4%	23.1%
45-64	26.6%	18.5%
65+	16.4%	17.3%

INTERPRETATION

A major risk to the investigator in health services research is to interpret the meaning of descriptive data. These data do describe patient encounters in eleven family physicians' practices in southern

TABLE 2

PROBLEM OR SYMPTOM FREQUENCY IN MAINE PRACTICES

Rank	*Twenty Most Common Problems or Symptoms*	*% of Visits*	*Cumulative %*
1.	Limited P.E., Check-Up, or Follow-Up	22.3%	22.3%
2.	General Physical Exam	8.1%	30.4%
3.	Problems of Face, Head, and Neck	7.0%	37.4%
4.	Pregnancy Exam	5.5%	42.9%
5.	Infections	4.4%	47.3%
6.	Hypertension	4.3%	51.6%
7.	Problems of Lower Extremity	2.7%	54.3%
8.	Abnormal Skin Reaction	2.7%	57.0%
9.	Throat Soreness	2.5%	59.2%
10.	Abdominal Pain	2.5%	62.0%
11.	Cough	2.2%	64.2%
12.	Wounds, Concussions, and Contusions	2.1%	66.3%
13.	Fatigue	2.0%	68.3%
14.	Gynecological Problems	2.0%	70.3%
15.	Cold	1.9%	72.2%
16.	Problems of Back	1.9%	74.1%
17.	Headache	1.6%	75.7%
18.	Immunization	1.6%	77.3%
19.	PAP Exam	1.4%	78.7%
20.	Counseling and Patient Education	1.4%	80.1%

TABLE 3

TWENTY MOST COMMON PATIENT PROBLEMS OR SYMPTOMS

	National Survey	*Maine Family Practices*
1. Problems of Lower Extremity	4.3%	2.2% (7)
2. Throat Soreness	4.3%	2.5% (9)
3. Problems of Back	3.7%	1.9% (16)
4. Cough	3.5%	2.2% (11)
5. Required or Limited P.E., Check-Up, or Follow-Up	3.4%	22.3% (1)
6. Visit for Medication	3.2%	1.3% (+20)
7. Cold	3.1%	1.9% (15)
8. Problems of Upper Extremity	3.1%	1.3% (+20)
9. Abdominal Pain	2.8%	2.5% (10)
10. Pregnancy Exam	2.6%	5.5% (4)
11. Headache	2.4%	1.6% (17)
12. Fatigue	2.2%	2.0% (13)
13. High Blood Pressure or Hypertension	2.1%	4.3% (6)
14. Weight Gain	2.0%	.2% (+20)
15. Wounds, Concussions, Contusions	2.0%	2.1% (12)
16. General Physical Exam	1.9%	8.1% (2)
17. Problems of Face, Head, and Neck	1.7%	7.0% (3)
18. Allergic or Abnormal Skin Reaction	1.6%	2.7% (8)
19. Vertigo	1.5%	.7% (+20)
20. Fever	1.5%	1.2% (+20)

TABLE 4

PRIOR VISIT STATUS

	National Survey	*Maine Family Practice*
Patient Seen for First Time:	12.2%	25.4%
Patient Seen Before for Current Problem	57.8%	50.4%
Patient Seen Before for Another Problem	30.3%	23.5%

TABLE 5

MAJOR REASON FOR THIS VISIT

Acute Problem	35.9%
Acute Problem, Follow-Up	11.3%
Chronic Problem, Routine	20.2%
Chronic Problem, Flare-Up	6.2%
Prenatal Care	5.8%
Postnatal Care	.5%
Postoperative Care	.4%
Well Adult-Child Exam	13.9%
Family Planning	2.2%
Counseling/Advice	.8%
Immunization	2.5%
Referred by Other Physician/Agency	.1%
Administrative Purpose	.1%
Other	4.0%

Maine. Comparison with the National Survey raises questions which must be pursued in order to explain why these differences exist. Descriptive epidemiology tells us where to look next. The age distribution of patients in the southern Maine practices is younger than in the National Survey. The physicians who participated in the survey performed by us, tended to be younger, and were recent products of the family practice residency program. If younger physicians generally have younger practices perhaps this could explain the difference in age distribution. Or perhaps the predominance of patients in the younger age bracket is related to the summer months of sampling

Table 6

Physicians' Principal Diagnoses

Rank	Fifteen Most Frequent Diagnoses	% of Visits	Cumulative %
1.	Normal Health	9.9%	9.9%
2.	Hypertension	8.5%	17.4%
3.	Bacterial Infection	5.3%	22.7%
4.	Prenatal Care	5.0%	27.7%
5.	Eczema, Dermatitis, Warts, Cysts, and Rashes	3.4%	31.1%
6.	Unknown	2.8%	33.9%
7.	Diabetes	2.5%	36.4%
8.	Trauma	2.5%	38.9%
9.	Viral Infection	2.2%	41.1%
10.	Allergic Reaction	2.1%	43.2%
11.	Otitis Media or Externa	1.8%	45.0%
12.	Neuroses	1.6%	46.6%
13.	Neoplasm	1.6%	48.2%
14.	Chronic Ischemic Heart Disease	1.5%	49.7%
15.	Innoculations, Vaccinations, and Immunizations	1.5%	51.2%

Table 7

Treatment, Service Ordered, or Provided

	National Survey	Maine Family Practices
None Ordered/Provided	10.6%	2.0%
General History/Exam	29.2%	60.0%
Lab Procedure/Test	17.1%	22.4%
X-Rays	5.8%	5.4%
Injection/Immunization	23.1%	5.7%
Office Surgical Treatment	7.6%	6.0%
Prescription Drug	60.3%	36.9%
Non-Prescription Drug		5.6%
Psychotherapy/ Therapeutic Listening	18.4%	2.7%
Medical Counseling/Advice		39.4%
Other	10.6%	3.3%

during which time there may be more younger tourists. Further studies would need to be done to explain why the age difference should exist.

Accepting that the aggregation of the presenting symptoms or problems is judgmental, there do seem to be differences in the practices of the southern Maine physicians. Visits for medication, visits for weight gain, visits for vertigo, and visits for fever are under-represented. These differences are probably genuine and one can speculate regarding the findings. Particularly knowing that the low rate of visits for medicines is matched by strikingly low rates of injections, immunizations, and ordering both prescription and non-prescription drugs, one must conclude that for whatever reason these eleven practices use and prescribe medications much less than the National Survey. Indeed there may be a trend in Maine or a trend among younger family physicians to withhold medications. It would be important to validate these findings and to determine the reasons for these differences. Are they related to the type of patient problem that is presented, the age of the physician, or something else? The difference is real but the meaning is not known through this survey. Table 7 in general raises a series of questions that relate to practice behavior.

Conclusion

During July 1978, eleven practices of family physicians in southern Maine were sampled for a one week period using a modified encounter form of the National Ambulatory Survey. Some significant differences were found including age distribution, the most common patient problems and symptoms at presentation, prior visits status, major reason for visits, and treatment and services ordered or provided. The survey was done at a time when Maine has many summer visitors and this may have changed the age distribution and the fact that 25% of the patients were seen for the first time. Other differences, specifically diagnostic category and the use of injections and medications are not so simply explained. For example, these eleven practices were significantly involved in providing prenatal care at a higher rate than the practices surveyed in the National Survey. Important next steps would be to critically examine these differences to uncover the significance. Furthermore, this information provides a rational basis for beginning to develop continuing education programs for family physicians.

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Preoperative Transfemoral Catheter Embolization of Head and Neck Tumors

L. Reed Altemus, M.D., Robinson L. Bidwell, M.D., John E. Knowles, M.D. and David K. Lovely, M.D.*

Catheter embolization of the external carotid artery is now recognized as a useful and safe means of controlling intraoperative hemorrhage encountered when attempting to remove certain vascular neoplasms of the head and neck. Embolization is usually performed shortly before surgery especially when less permanent materials are used for endovascular occlusion. Methods and materials used vary according to the preferences and experience of the radiologist. Recently, more permanent therapeutic embolization has been achieved using liquid adhesives. For the most part, however, gelatin sponge (Gelfoam®) remains the most widely used material for embolization, a preference relating to its availability, ease of injection and proven biocompatibility. A disadvantage of Gelfoam is its tendency to shrink leading to re-canalization of vessel lumens. This undesirable characteristic can be minimized by scheduling surgery shortly after embolization.

At the Maine Medical Center, applications of external carotid artery embolization have been limited to preoperative devascularization. The following report summarizes our experience with 3 head and neck tumors.

Case Reports

Case 1. Y.N., a 68-year-old female, presented with a large mass involving the left side of her scalp. In 1960, a hemangioblastic meningioma was removed from this area. She remained free of symptoms until seizures developed two years prior to her current admission. On physical examination, a very large pulsatile mass was visible covering the left calvarium. Loud bruits were audible over the entire region. On examination, her mental status was felt satisfactory but a mild right hemiparesis was noted. A chest film demonstrated rib destruction adjacent to a left chest wall mass. Skull films showed extensive osteolysis beneath the scalp mass (Fig. 1). Biopsies of both chest wall and scalp revealed angioblastic meningioma. Her hospital course was characterized by gradual mental deterioration, confusion, and increasing right hemiparesis. This prompted consideration of surgical removal of the mass following angiographic assessment and possible catheter embolization. Angiography established that the major blood supply to the tumor was derived from the extracranial circulation. Seventy Gelfoam emboli were injected into the left external carotid artery (Figs. 2A-2D). Although all extracranial carotid contributions were totally embolized, feeding vessels also arose from the left middle cerebral artery. These could not be safely embolized. Following embolization she remained stable without obvious progression of her neurologic deficit. On the sixth day following embolization, surgical removal of the tumor was attempted. The resection was difficult necessitating 14 units of blood. Her immediate postoperative response was satisfactory, but within hours, she lapsed into deep coma and died seven days later. A post mortem examination was performed, and extensive hemorrhagic infarction of the entire left hemisphere was found. Venous obstruction as a possible cause was excluded by careful inspection of the veins and sinuses draining the left hemisphere. No Gelfoam emboli were found within the venous circulation. Metastasis to the mediastinum was also discovered.



Fig. 1, Case 1. Lateral view of the skull showing extensive osteolysis of the left calvarium. Craniotomy defects and large vascular channels also noted (arrows).

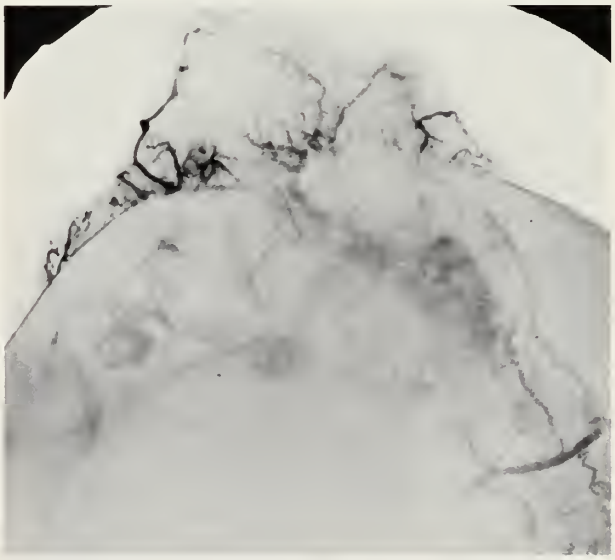


Fig. 2A, Case 1. Late arterial phase in lateral projection showing the large vascular soft tissue component extending above the calvarium.

COMMENT: This unfortunate outcome may possibly be related to the dual blood supply of the tumor. Contributions from both the extracranial and intracranial circulations were involved. In removing the tumor, which was attached to the brain surface,

*From the Maine Medical Center, Portland, Maine 04102.



Fig. 2B, Case 1. Pre-embolization left external carotid angiogram demonstrating the extent of neovascularity derived from the extracranial circulation.



Fig. 2C, Case 1. Subtraction film (bone subtracted) of 2B showing more clearly the plethora of feeding arteries.

numerous middle cerebral artery branches had to be sacrificed. Further, collateral circulation by the transdural route was rendered inoperative when the extracranial circulation was embolized. These factors most likely contributed to progressive brain swelling and infarction.

Case 2. B.G., an 11-year-old male, was admitted to the hospital complaining of progressive nasal obstruction of 2 years' duration. A large redish mass was visualized in the nasopharynx. Conventional radiographs supported the clinical diagnosis of juvenile nasopharyngeal angiofibroma (Fig. 3A)[4]. He was placed on estrogen therapy and arrangements were made for preoperative angiography followed by catheter embolization if angiographic



Fig. 2D, Case 1. Post-embolization selective left external carotid angiogram after the injection of 70 Gelfoam emboli. Contributions from the external carotid artery totally occluded.

findings proved favorable. A percutaneous transfemoral carotid angiogram was performed. Both the extracranial and intracranial carotid circulation were visualized. The tumor proved to be extremely vascular and primarily supplied by the right external carotid artery (Fig. 3B). A polyethylene catheter (I.D. 1.12 mm., O.D. 1.66 mm.) was advanced into the right internal maxillary artery beyond the origin of the superficial temporal branch. Thirty Gelfoam emboli were injected under fluoroscopic control. No further emboli were injected when contrast material refluxed into the proximal portion of the internal maxillary artery (Fig. 3C). The following day a right internal maxillary artery ligation was performed and complete surgical removal of the tumor accomplished using the transpalatine approach. A scant 250 cc. of blood was lost during surgery. The postoperative period was uneventful, and the patient was discharged on the 4th postoperative day.

COMMENT: This case illustrates an optimal therapeutic result. Success of embolization relates to the confinement of the tumor to the nasopharynx, its unilateral blood supply from a single internal maxillary artery and the ability to subselectively catheterize the artery permitting distal endovascular occlusion of the tumor vascular bed.

Case 3. D.B., a 15-year-old male, was admitted for evaluation of nasal obstruction secondary to a redish tumor visible within the nasopharynx and nasal antrum. Angiography was performed on the day following admission confirming the presence of a large vascular mass in the nasopharynx extending into the sphenoid sinus. The vascular appearance of the neoplasm was typical for angiofibroma (Figs. 4A and 4B) and 36 Gelfoam emboli were injected into the left internal maxillary artery (Figs. 4C).[1-4] The major portion of the vascular bed was rendered avascular but contributions from a proximal branch of the external maxillary artery could not be embolized due to transient eye symptoms experienced during the procedure (Fig. 4C). The following day the left internal carotid artery was ligated and total removal of the angiofibroma was accomplished using the transpalatine approach. Bleeding was encountered requiring 5 units of blood replacement. The postoperative period was uneventful. The nasal pack was removed on the fifth postoperative day and discharge occurred 3 days later.

COMMENT: Total devascularization by catheter embolization was not accomplished in this case but a large tumor extending beyond the nasopharynx could be excised with only moderate intraoperative hemorrhage. In the pre-embolization era, angio-



Fig. 3A, Case 2. Film of the lateral neck showing large soft tissue mass within the nasopharynx (arrows).



Fig. 3B, Case 2. Selective right external carotid angiogram (late arterial phase) visualizing vascular angiofibroma.

fibromata of this extent were removed with difficulty; often incompletely due to excessive bleeding encountered during surgery. Transient monocular blurring experienced during embolization limited total occlusion of all feeding arteries (Fig. 4C). The reason for this symptom remains unexplained, but possible causes are spasm, proximal migration of tiny Gelfoam fragments or the origin of the ophthalmic artery from the meningeal artery. This anatomic variant should always be established by angiograms obtained prior to embolization.

Discussion

The first therapeutic endovascular occlusive procedure was performed in 1904, a surprisingly early date in view of the belated accceptance of this procedure as a worthwhile preoperative or definitive therapeutic endeavor. With the development of transfemoral catheterization by Seldinger technique together with further refinements in instrumentation and television fluoroscopy, therapeutic neuroradiology developed via the femoral route. Arteriotomy of the cervical external carotid artery was no longer necessary and superselective catheterization using small diameter catheters soon followed.[2] During the same period, qualities of embolized materials improved and currently there are a plethora of techniques and materials available to block blood vessels. They include balloon catheters, silastic spheres, gelatin sponge (Gelfoam), polyvinyl alcohol foam (Ivalon®), lipolized dura mater, and liquid adhesive substances, such as Isobutyl-6-Cyanocrylate. The selection of approach and embolic material used depends upon therapeutic objectives, availability of the materials, ease of introduction,



Fig. 3C, Case 2. Post-embolization selective right external carotid angiogram. Vascular bed completely embolized.

safety of the methodology, and preferences of the angiographer. Injected substances should be biologically compatible, lead to permanent occlusion



Fig. 4A, Case 3. Pre-embolization left external carotid angiogram. Hypervascularity typical for juvenile angiofibroma. Posterior extent and dual blood supply from two large arteries shown (arrows).



Fig. 4B, Case 3. Pre-embolization subtraction film. Extent of vascularity more clearly defined.

without re-canalization, and provoke antegrade thrombosis of the distal tumor vascular bed which restricts revascularization by the non-embolized collateral circulation.



Fig. 4C, Case 3. Post-embolization external carotid angiogram (subtraction film). Devascularization not complete after 36 Gelfoam emboli. A large posterior feeding artery is still patent (arrow).

Irrespective of the technique selected the objective common to all is complete endovascular occlusion without sequelae. Relative to head and neck tumors supplied primarily by the external carotid circulation, most investigators favor preoperative embolization using Gelfoam or Ivalon injected subselectively; that is, into the most distal segments of feeding arteries. Furthermore, precautions must be taken to prevent proximal migration of injected emboli. These prerequisites can be met by using either small diameter catheters for subselective catheterization or employing balloon catheters which can be inflated to prevent proximal migration of injected material. Future developments in interventional Neuroradiology can be anticipated and intracranial applications now under extensive investigation may revolutionize our traditional approach to the management of aneurysms and arteriovascular malformations.[1]

Acknowledgments

The authors would like to thank Dale McLellan, R.T. and Patricia Norton, R.N. for their assistance doing the embolization procedures.

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Continued on Page 375



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When painful spasm is the presenting symptom...



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Demonstrated smooth muscle relaxant activity.

In this double-blind study, twenty patients having G.I. series and exhibiting spasm were randomly selected to receive either 2 cc. of Bentyl or sodium chloride intramuscularly. Ten minutes after the injection another radiograph was taken . . .

. . . Bentyl produced definite relaxation in 8 of 10 patients. The sodium chloride produced relaxation in only 3 of 10. No side effects occurred in either group of patients.



Pylorospasm has almost totally blocked passage of barium meal.



Barium meal beginning to pass 10 minutes after intramuscular injection of 20 mg. Bentyl.

"The correlation of spasm relief and drug given was excellent."

*This drug has been classified "probably" effective in treating functional bowel/irritable bowel syndrome.

†See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964.

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Brief Summary

INDICATIONS

Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the following indications as "probably" effective:

For the treatment of functional bowel/irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

THESE FUNCTIONAL DISORDERS ARE OFTEN RELIEVED BY VARYING COMBINATIONS OF SEDATIVE, REASSURANCE, PHYSICIAN INTEREST, AMELIORATION OF ENVIRONMENTAL FACTORS.

For use in the treatment of infant colic (syrup)

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis; toxic megacolon complicating ulcerative colitis, myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: Autonomic neuropathy. Hepatic or renal disease. Ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension. Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia, urinary hesitancy and retention; blurred vision and tachycardia; palpitations; mydriasis; cycloplegia; increased ocular tension; loss of taste; headache, nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons, and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs.

Usual Dosage: Bentyl 10 mg. capsule and syrup: *Adults*: 1 or 2 capsules or teaspoonfuls syrup three or four times daily. *Children*: 1 capsule or teaspoonful syrup three or four times daily. *Infants*: ½ teaspoonful syrup three or four times daily. (May be diluted with equal volume of water.) Bentyl 20 mg.: *Adults*: 1 tablet three or four times daily. Bentyl Injection: *Adults*: 2 ml (20 mg.) every four to six hours intramuscularly only. NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE: The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

Product Information as of October, 1978.

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and 30 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

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and 50 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

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J9AR13

Oral Complications Secondary to Radiotherapy to the Head and Neck Area

ALAN J. HICKEY, D.M.D.*

As better and more effective techniques of surgery, radiotherapy, and chemotherapy or combinations thereof are developed, the life expectancy of the patient with cancer of the head and neck is often markedly increased.[1] Due to this increased life expectancy, the long term type of complications that can follow radiotherapy to the head and neck, have time to develop. Since patients will often seek advice from the family physician and other medical specialists regarding care that they require relative to their oral problems, it is imperative that the physician be familiar with the development, prevention, and treatment of possible oral complications. The most common complications are radiation caries or decay of the remaining teeth, generalized sensitivity of the teeth to temperature change, xerostomia, and osteoradionecrosis.

The potential for developing osteoradionecrosis of the bone must always be considered. Radiation to the head and neck will cause a permanently reduced blood supply resulting in decreased healing capacity of both soft tissue and bone, which can allow development of spontaneous osteoradionecrosis, or osteoradionecrosis percipitated by a traumatic episode. As the dose of radiation increases, the probability of developing osteoradionecrosis and other complications increase.[2] Thus, it is important to consult with the radiotherapist so that not only the dose is known, but type of radiation, method of delivery, and exact location and extent of fields of radiation. Any type of oral surgical procedure, such as tooth extraction, periodontal surgery, or other elective procedure should be avoided in radiated areas. If the teeth are non-restorable, if possible they should be extracted prior to initation of radiotherapy with adequate healing time allowed. Healthy teeth should not be extracted, even if they are directly in the field of radiation, but should be maintained with a comprehensive fluoride program, as described later, and routine dental care. If teeth are extracted after radiotherapy, the patient will often lose all or part of the jaw with the necrosis progressing until bone is encountered that has not been irradiated (Fig. 1).

If osteoradionecrosis does develop spontaneously, it should be managed conservatively with irrigation, gentle debridement, antibiotics, and good oral hygiene. If an area is curretted, or surgically manipulated to remove obvious necrosis, it will often only create more extensive necrosis problems. By using the conservative management of the region, healing will take place in most cases, especially if recognized early prior to development of gross infection in the area.



Fig. 1. This 43-year-old male had squamous cell carcinoma of naso-labial fold with metastasis to cheek and both sides of neck. He was treated with 7200 rads of radiation through parallel opposed and anterior fall off fields, and has been free of disease for six years, but he lost entire mandible over a four-year period from osteoradionecrosis. Reconstruction would be extremely difficult, if not impossible, due to lack of available tissue locally, and poor healing, secondary to radiation.

Since radiation to the head and neck area also destroys salivary gland function, thereby reducing salivary flow to the oral cavity, eating and swallowing may become difficult for the patient. Extensive caries are often prevalent following radiation if the teeth are not protected by a comprehensive fluoride program after treatment (Fig. 2 and 3). The method that has shown long term effectiveness in these patients, is the construction of custom made fluoride carriers* to fit over the remaining teeth with the daily

*Associate Staff, Prosthodontics, Maine Medical Center, Portland, Maine 04102.

*Sta-Guard Mouthguard Material, Buffalo Dental Manufacturing Co., Brookline, N.Y.



Fig. 2. 71-year-old male with moderate radiation caries. This is classical appearance along gingival margins of teeth. Even with good restorations, these areas will redecay without additional fluoride protection.



Fig. 3. 65-year-old male. These teeth were intact two years ago, prior to treatment, but patient would not use fluoride, and had very poor hygiene. Teeth are presently grossly decayed and are nonsalvageable.

application of 1% Sodium Fluoride Gel** (Fig. 4). Sensitivity of the teeth to temperature change is a frequent complaint, which can also be eliminated with this fluoride program. One of the most common and annoying side effects of head and neck irradiation is moderate to severe xerostomia. The application of an artificial saliva*** can sometimes reduce the discomfort from this condition.

In most cases, the majority of the population that develops cancer of the head and neck area is older, and may be either edentulous or partially edentulous, and need prosthetic replacement of missing teeth to function adequately. Due to the problems of dryness, tissue sensitivity and potential for soft tissue and bony breakdown, hydroscopic impression materials should not be used, since they may cause tissue damage. Most of these patients can successfully wear prosthetic replacements (dentures and/or partials), but need to be seen and followed extremely closely by a professional that is familiar with problems that may develop, so that the proper preventive steps are taken.

Since the effects of radiation are progressive and persist throughout the lifetime of the patient, it is important for medical professionals in many disciplines, to be familiar with the possible oral complications and their treatment. Prevention is of utmost importance to avoid major disabilities, both functionally and aesthetically. Dental management of the patient with cancer, especially when the disease process involves the head and neck region, should be an integral part of the patient's overall medical treatment plan.



Fig. 4. 19-year-old female who received radiation six and a half years ago. She has used fluoride daily, and has good hygiene, with no carious lesions evident. This result is expected in all cases with patient cooperation, a good fluoride program, and follow-up.

**Emerson Laboratories, Pharmaceutical Specialties, Dallas, Texas 75221.

***Xerolube—Scherer Pharmaceutical Corp., Dallas, Texas 75240.

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43 Baxter Blvd., Portland, Maine 04101

New MMA Mailing Address, Hours of Coverage - - -

The office of the Maine Medical Association was moved from Brunswick to Augusta on August 15. Renovations for meeting space and additional parking are under way. The new mailing address is 524 Western Avenue, Augusta 04330. Please note the new telephone number also -- 622-3374.

Members attending meetings at the new headquarters should look for a circular drive next to the Trends Furniture store on Western Avenue (Route 202), approximately 9/10 of a mile west of the Augusta turnpike interchange. The building itself is a contemporary split level house with grey shingles, brick accent section and Cape Cod blue trim.

At the present time, and as an incentive in the retention of able, trained personnel, the entire office staff is commuting by car pool from the Brunswick area and the office is open 8 to 5, Monday through Thursday. On Fridays the office is occupied only by the Executive Director and if he is absent - committee meeting, legislative hearing, or other Association business - the phone will not be covered. When finances permit, additional Friday coverage will be secured.

Massachusetts Blue Shield, Medical Society Separated - - -

The statutory relationship between Massachusetts Medical Society and the state's Blue Shield plan was terminated June 30. Action came with the signing of legislation by Gov. Edward J. King.

Commenting on the legislation, John Larkin Thompson, president of the plan, said "We hope the medical community will continue to participate in Blue Shield programs and join us in a renewed commitment to our Massachusetts subscribers."

A spokesman for MMS said he now would like to see the legislature and governor pass a bill that would remove the "lock-in" of physicians to Blue Shield. The contract now requires physicians to accept assignment as payment in full, and provides reimbursement only for member physicians.

The society has challenged the "lock-in" in court, and has sponsored a bill calling for reform of the contract.

Influenza Immunization Program For High-Risk Persons - - -

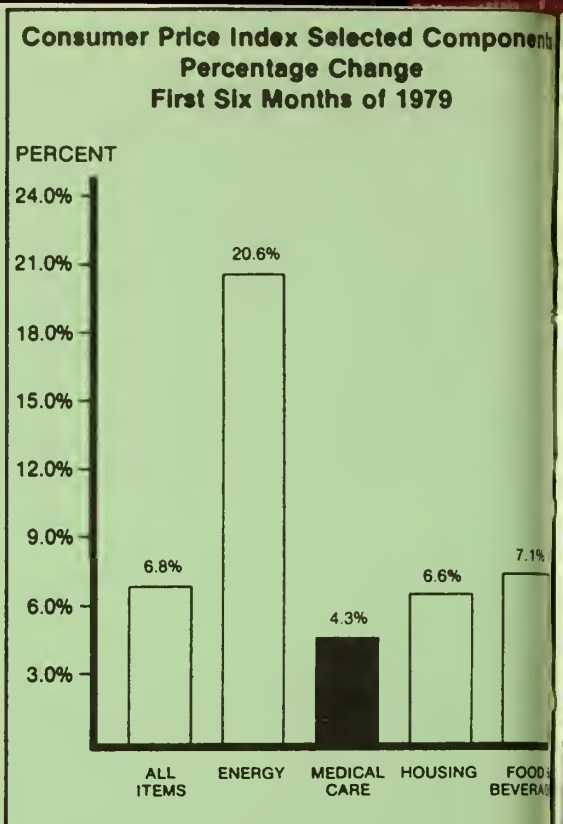
The Maine Department of Human Services has received a federal grant to conduct an influenza program for persons who are at high-risk as defined by the United States Public Health Service, Advisory Committee on Immunization Practices.

The Maine Immunization Program will provide, at no charge, the vaccine in ten dose vials for administration to any provider who is interested in offering this service. The supply is limited and The Bureau of Health will fill requests on a "first come, first served" basis until the supply is exhausted. They currently have both the adult (whole) and youth (split) formulas available.

If you are interested in obtaining a supply of influenza vaccine or have any questions regarding the Program, please contact the Maine Department of Human Services, Bureau of Health, Augusta. Tel.289-3746

Medical Care Costs Trail Inflation - - -

The rate of increase in medical care costs trailed the overall inflation rate during the first six months of 1979 according to American Medical News.



American Medical Association, Center for Health Services, Research and Development.

Osteopaths Vote To Allow AMA Membership - - -

Delegates of the American Osteopathic Association voted recently to allow their members to join the AMA and specialty societies outside the osteopathic profession. AOA President Dale Dodson, D.O., said the abrupt policy shift was the result of growing confidence. "We know that the pluralism between osteopathic and allopathic medicine is going to be maintained," he said. "We have outgrown our paranoia about being swallowed up by the AMA."

The AOA House also raised dues to $275 and called for immediate action "to increase regular membership dues by $100 annually," with 50% to be "placed in reserve for alleged tax liability and other emergencies."

Michigan Medical Society Is Target Of FTC Complaint - - -

A charge of conspiring to fix or stabilize fees has been brought against the Michigan State Medical Society by the Federal Trade Commission. According to the complaint, the society solicited "proxies" from members to authorize termination of contracts with Blue Cross and Blue Shield of Michigan and Michigan Medicaid if they didn't adopt reimbursement policies acceptable to the society.

Maine Medical Education Foundation Grants Loans to Maine Medical Students

Loans totaling more than $64,000 have been awarded by the Maine Medical Education Foundation to 62 Maine students attending medical school, Dr. Ferris S. Ray, Chairman of the MMA's Committee on Recruitment, Aid and Placement announced recently. Last year 159 Maine students attended medical school in the United States and Canada.

Medical school costs of $13,000 to $15,000 per year are now common, with student budgets at some institutions running in excess of $20,000 per year.

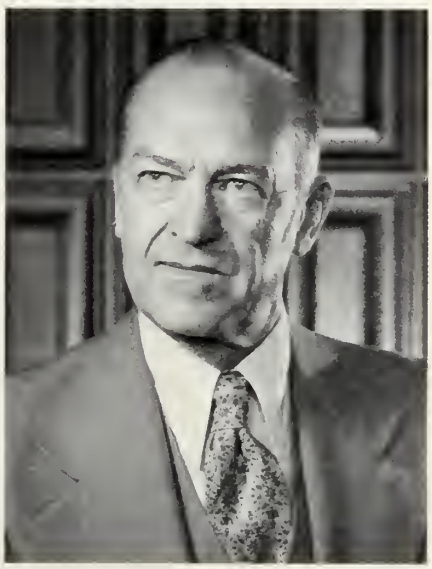
"Even higher medical school costs are anticipated in the near future," said Dr. Ray, "as federal government cuts in capitation grants to medical schools increase the portion of the financial cost of a medical education which the student must bear personally. Today, the Maine Medical Education Foundation, a trust fund of the MMA, has more than $450,000 outstanding in loans."

The committee's placement function in the past two years has brought together 49 physicians with Maine towns desiring to secure additional medical coverage.

President

Maine Medical Association

1979-1980



BRINTON T. DARLINGTON, M.D.

Brinton T. Darlington, M.D., of Augusta, Maine, became the 130th President of the Maine Medical Association at the 126th annual session banquet on June 18, 1979. He served as President-elect of the Maine Medical Association from 1978-1979.

Dr. Darlington was born in Olean, New York on January 7, 1922, son of J. Leon and Martha T. Darlington. He was graduated from Ohio University in 1943 and received his medical degree from State University of New York Upstate Medical Center, Syracuse in 1945. He interned at St. Luke's Hospital in Cleveland, Ohio and served a residency at the U.S. Marine Hospital in Staten Island. In 1952, he located in Augusta.

He is a member of the Kennebec County Medical Association, the Maine Medical Association, the American Medical Association, and is a member of the Liaison Committee Between the Maine Bar Association and the Maine Medical Association, the M.M.A.'s Building Finance Committee, the Long-Range Planning Committee and the Committee on Legislation of which he was chairman for many years. Dr. Darlington was a former Vice President of the American Lung Association, former President of the Maine Thoracic Society, the Maine Lung Association, the Maine Society of Internal Medicine and former member of the M.M.A.'s Committee on Membership and the School Health Committee.

Dr. Darlington has served as Alternate Delegate to the AMA since 1974, and was re-elected to serve another term from Jan. 1, 1980 to Dec. 31, 1981.

Executive Committee Members Elected at the 126th Annual Session of the Maine Medical Association

Rockport, Maine — June 16-19, 1979

President
Brinton T. Darlington, M.D.
Augusta

President-elect
Robert E. McAfee, M.D.
Portland

First District
Robert F. Ficker, M.D.
Kennebunkport

Second District
William H. Maxwell, M.D.
Portland
Executive Committee Chairman

Fifth District
Paul A. Brinkman, M.D.
Farmington

Sixth District
Donald M. Robertson, M.D.
Harrington

Ninth District
Craig W. Young, M.D.
Presque Isle

Delegate to the AMA
Robert E. McAfee, M.D.
Portland

Alternate Delegate to the AMA
Brinton T. Darlington, M.D.
Augusta

Speaker of the House
George W. Bostwick, M.D.
Newcastle

Dr. Robert E. McAfee was elected President-elect; Dr. George W. Bostwick, Speaker of the House; Dr. Robert E. McAfee, Delegate to the AMA and Dr. Brinton T. Darlington, Alternate Delegate to the AMA. The following physicians were elected to the Executive Committee: Dr. Robert F. Ficker, First District (1979-1982); Dr. William H. Maxwell, *Chairman* of the Executive Committee (1979-1980); Dr. Paul A. Brinkman, Fifth District (1979-1982); Dr. Donald M. Robertson, Sixth District (1979-1982); and Dr. Craig W. Young, Ninth District (1979-1981), to complete Dr. Harry M. Helfrich, Jr.'s unexpired term.

DR. McAFEE, of Portland, was born there on August 25, 1935, son of Harold G. and Elizabeth H. McAfee. Dr. McAfee was graduated from Deering High School in 1952, Bates College in 1956 and received his medical degree from Tufts University School of Medicine in 1960. He interned at the Maine Medical Center and served a residency in General Surgery from 1961 to 1965. Since 1965, Dr. McAfee has been attending surgeon at the Maine Medical Center and the Mercy Hospital, where he has been chief of surgery since 1974.

He is a member of the Cumberland County Medical Society, the Maine Medical Association, the American Medical Association, and is certified by the American Board of General Surgery. He is a Past President of the CCMS.

Dr. McAfee was formerly President of the American Cancer Society, Maine Division, Inc., Chairman of its Medical Affairs Committee and is currently a member of the National Board of Directors; was Chairman of the State Advisory Committee and State Ambulance Licensure Board of the Emergency Medical Services Division, Department of Health and Welfare; is a long-time member of the Committee on Recruitment, Aid and Placement of the Maine Medical Association, serving as Chairman for several years; and is on the M.M.A.'s Long-Range Planning Committee.

Dr. McAfee served as Alternate Delegate to the AMA from 1972 to 1974 and has been Delegate to the AMA since 1974. He was re-elected to serve another term from Jan. 1, 1980 to Dec. 31, 1981. He is currently Chairman of the New England delegation and has been elected Vice Chairman of AMA Council on Long-Range Planning for the current year.



DR. MCAFEE



DR. FICKER



DR. MAXWELL

DR. FICKER, of Kennebunkport, was born in Brooklyn, New York on April 14, 1916, son of Robert V. and Emily Kaiser Ficker. He was graduated with a B.A. degree from Bard College of Columbia University in 1939 and received his medical degree from New York University College of Medicine in 1943. He interned at Bellevue Hospital in New York from 1942 to 1943 and at the Brooklyn Hospital from 1943 to 1944. Dr. Ficker served as a Captain in the U.S. Army Medical Corps for three years. He took a post-graduate course in Internal Medicine at New York University from 1946 to 1947, and then practiced in Wanaque and Ogdensburg, New Jersey before coming to Kennebunkport in 1953. He has been on the staff of Webber Hospital in Biddeford since 1953.

He is a member of the York County Medical Society, serving as President in 1960, the Maine Medical Association and the American Medical Association. Dr. Ficker is a current member of the Committee on Health Care Financing, served on the M.M.A. Peer Review Committee and was Chairman of the School Health Committee from 1958 to 1959. In addition, Dr. Ficker has been a member of the M.M.A. House of Delegates for fifteen years.

Dr. Ficker was a member of the Executive Committee of the M.M.A. for the First District from 1969 to 1976, serving as Chairman from 1973-1974.

DR. MAXWELL, of Portland, was born there on February 16, 1939, son of Irving W. and Florence D. Maxwell. He was graduated from Middlebury College and received his medical degree from Boston University School of Medicine in 1966. He interned in Surgery at Boston University Medical Center from 1966 to 1967, served in the U.S. Army as a Captain from 1967 to 1969 and served a residency in Surgery and ENT from 1970 to 1973. He located in Portland in 1973 and is on the active staff at the Maine Medical Center and Mercy Hospital and on the consulting staff at the Bridgton Hospital.

He is Vice President of the Cumberland County Medical Association, a member of the Maine Medical Association and the American Medical Association, President of Medical Mutual Insurance Company of Maine and a member of its Board of Directors, and member of the National Committee on Legislative Communications for American Council of Otolaryngology.

Dr. Maxwell has been a member of the Executive Committee of the M.M.A. for the Second District since 1977, completing Dr. Douglas R. Hill's unexpired term.

DR. BRINKMAN, of Farmington, was born in Resht, Iran on June 17, 1932, son of Dr. and Mrs. Harry Brinkman. Dr. Brinkman was graduated from Bowdoin College in 1954 and received his medical degree from Tufts University School of Medicine in 1958. He interned and served a residency at the Maine Medical Center. He has practiced in Farmington since 1963 where he is affiliated with the Franklin County Memorial Hospital.

Dr. Brinkman is a member of the Franklin County Medical Society and the Maine Medical Association.

DR. ROBERTSON, of Harrington, was born in Brockville, Ontario, Canada on January 29, 1929, son of Dr. D.W. and Olive G. Robertson. Dr. Robertson attended school in Brockville before going on to the University of Ottawa, graduating in Medicine in 1953 at the age of 23. Following internship, he practiced in Eastern Ontario until 1966, at which time he moved to Maine. He was initially associated with the Maine Coast Memorial Hospital, and opened and operated the Milbridge Medical Center until 1975. Since 1968, he has been on the Staff of the Down East Community Hospital in Machias, practicing General Surgery and Gynecology



DR. ROBERTSON



DR. BOSTWICK

and some General Practice. He is an associate member of the medical staff of the Eastern Maine Medical Center.

Several years before leaving Canada he founded the St. Lawrence Medical Clinic, which continues as a multi-specialty group practice in Eastern Ontario. Since coming to Maine he has been involved in the development of Down East Health Services, Inc., which operates a Maternal and Infant Care program, a Family Planning program, a Children's program, and a WIC program in Washington and Hancock counties. He is a member of the board of that organization. He was also involved in the development of the Washington County Health Plan, which continues to provide pre-paid medical care for medically indigent patients in Washington County. Since 1972, he and his associates at Down East Community Hospital have offered a rotation in Rural Medicine for fourth year medical students, which has attracted about 75 students over the years. Several of these students have returned to residency programs in Maine, and at least two of them have gone into practice in Maine this year.

Several years ago he was involved with many other physicians in the development of a committee to promote a medical school for Maine, and became Chairman of that Committee. He is Director of Professional Education at the Down East Community Hospital.

He is a member of the Washington County Medical Society and the Maine Medical Association. Dr. Robertson is a member of the M.M.A.'s Committee on Recruitment, Aid & Placement and Rural Health Committee.

In addition to his professional interests, his hobbies are boating, especially on salt water, books, and cooking.

DR. YOUNG, of Presque Isle, was born in Buffalo, New York on August 18, 1942, son of William and Madelaine Young. He was graduated from Western Reserve University and received his medical degree from Georgetown University School of Medicine in 1972. Dr. Young served a Surgical Internship, followed by a Residency in Ophthalmology and Fellowship in Cornea and External Disease at the University of Iowa. He currently has hospital appointments at Cary Medical Center, A. R. Gould Memorial Hospital and the University of Iowa. He practiced in Iowa City from 1972 to 1977, when he located in Presque Isle.

He is a member of the Aroostook County Medical Association and the Maine Medical Association. Dr. Young is a member of the M.M.A.'s Committee on Government Health Activities and the Committee on Health Care Financing.

COMBINATION CHEMOTHERAPY OF ADVANCED, DIFFUSE, NON-HODGKIN'S LYMPHOMA: RESULTS WITH CYCLO-PHOSPHAMIDE, ADRIAMYCIN, VINCRISTINE, PREDNISONE, AND BLEOMYCIN (CHOP-BLEO)

Continued from Page 352

treatment of lymphomas: Southwest Oncology Group studies. Cancer Chemotherapy Rep 6 (Part 3): 375-380, 1975.

23. Bunn, P.A., Jr., Schein, P.S., Banks, P.M., DeVita, V.T., Jr.: Central nervous system complications in patient with diffuse histiocytic and undifferentiated lymphoma: Leukemia revisited. Blood 47:3-10, 1976.
24. Zuckerman, K., Skarin, A., Pitman, S., Rosenthal, D., Canellos, G.: High-dose methotrexate with citrovorum factor (MTX/CF) in the treatment of advanced non-Hodgkin's lymphoma (NHL), including CNS involvement. Blood 48:983, 1976.



CONTINUING MEDICAL EDUCATION IN MAINE

Conferences and Workshops

Title: **Family Medicine—Update**
Date: September 24-26, 1979
Location: Samoset Resort Inn, Rockport
Sponsor: Medical Care Development, Inc.
Credit: AMA Category I—15 hours; AAFP (prescribed)—15 hours
Reg. Fee: $150.00
For further information contact Gerald Goold; 622-7566

Title: **State of Maine Academy of Family Physicians Annual Meeting—Scientific Session**
Date: December 1, 1979
Location: Portland, Maine
Sponsor: State of Maine Academy of Family Physicians
Credit: AAFP (prescribed)—3 hours
For further information contact Roger E. Condit, M.D., Farmington, Maine; 778-6521

Hospital Activities

Augusta General Hospital
Augusta, Maine

Sept. 25, 1979: **Visiting Professor—Endocrinology**
7:30-9:30 a.m. Burritt Haag, Tufts University School of Medicine

Oct. 23, 1979: **Care of the Adolescent in the Hospital**
7:30-8:30 a.m. John F. Goodrich, M.D., AGH

Programs have been certified AMA Category I and AAFP (prescribed). For further information contact Mrs. Nancy York; 623-4711. Programs may be viewed over ITS.

Augusta Mental Health Institute
Augusta, Maine

Oct. 4, 1979
Issues in Geriatric Psychiatry I: Normal and Pathological Behavior in the Elderly 10-11:30 a.m.
Issues in Geriatric Psychiatry II: Depression, Dementia and Paranoia 1:30-3 p.m.
Kenneth Nobel, M.D., Harvard Medical School

Oct. 18, 1979
The Therapeutic Contract 10-11:30 a.m.
1) Analysis of Resistance 1:30-3 p.m.
2) The Termination Triad
Edward Messner, M.D., Harvard Medical School

The 10-11:30 a.m. Sessions are Grand Rounds; 1:30-3 p.m. Sessions are Inpatient Psychiatry Courses. All programs have been certified AMA Category I. For further information contact Pauline H. Soper; 622-3751

Eastern Maine Medical Center
Bangor, Maine

Every Mon.	EEG Conference	12-1 p.m.
Every Mon.	Surgical Service—Chief's Rounds	5-6 p.m.
4th Mon.	ENT Section Meeting	12-1 p.m.
4th Mon.	Neurosurgery Section Meetings	4-5 p.m.
3rd Tues.	Dermatology-Pathology Conference	5-6 p.m.
3rd Tues.	Dermatology Section Meeting	6-7 p.m.
4th Tues.	Pulmonary Medicine Section Meeting	8-9 a.m.
1st Wed.	Hematology/Oncology Meeting	8-9 a.m.
Every Wed.	Tumor Clinic Conference	2-5 p.m.
Every Wed.	Radiology Conference (1) Ultrasound/Nuclear Medicine (2) Radiology Film Review (3) Neuroradiology (4) Teaching File Conference	5-6 p.m.
1st Thurs.	Ophthalmology Section Meeting	7:30-8:30 a.m.
	OB-GYN Conference (1) Pathology (2) GYN Analysis (3) OB-Pediatric Combined (4) In-Service and Education	8-9 a.m.
Every Thurs.	Pediatric Grand Rounds	9-10 a.m.
Every Thurs.	Medical Service Conference	10-11 a.m.
Every Thurs.	Cardiology Conference	11a.m.-1 p.m.
2nd Thurs.	Orthopedic Grand Rounds	7:45-8:45 a.m.
4th Thurs.	Orthopedic Service Meeting	7:30-9 a.m.
4th Thurs.	Surgical Service Death Review	7:45-8:45 a.m.
Every Thurs.	Psychiatric Service Grand Rounds	10-11 a.m.
4th Thurs.	Urology Section Conference	7:30-8:30 a.m.
Every Fri.	Neurology Grand Rounds	8-9 a.m.

Visiting Professor Program:

2nd Thurs.	Medical Service Visiting Professor	10 a.m.-5 p.m.
2nd Thurs.	Anesthesia Service Visiting Professor	7-8 a.m.
3rd Thurs.	OB/GYN Service Visiting Professor	10 a.m.-4 p.m.
Saturdays	Surgery Service Visiting Professor	8 a.m.-Noon
4th Thurs.	Pediatric Service Visiting Professor	10 a.m.-5 p.m.
as scheduled	Orthopedic Service Visiting Professor	
as scheduled	Family Practice Visiting Professor	
as scheduled	Psychiatric Service Visiting Professor	
as scheduled	Radiology Service Visiting Professor	

All activities have been certified AMA Category I. For further information contact Robert H. Brown, M.D., Chairman, Medical Education Committee; 947-3711, Ext. 330.

A.R. Gould Memorial Hospital
Presque Isle, Maine

Oct. 6, 1979: **Burn Seminars**

8:30 a.m.-3 p.m. Richard Treet, M.D., Brook Army Hospital, San Antonio, Texas

This program has been certified AMA Category I. For further information, contact Raymond Giberson, M.D.; 769-8071

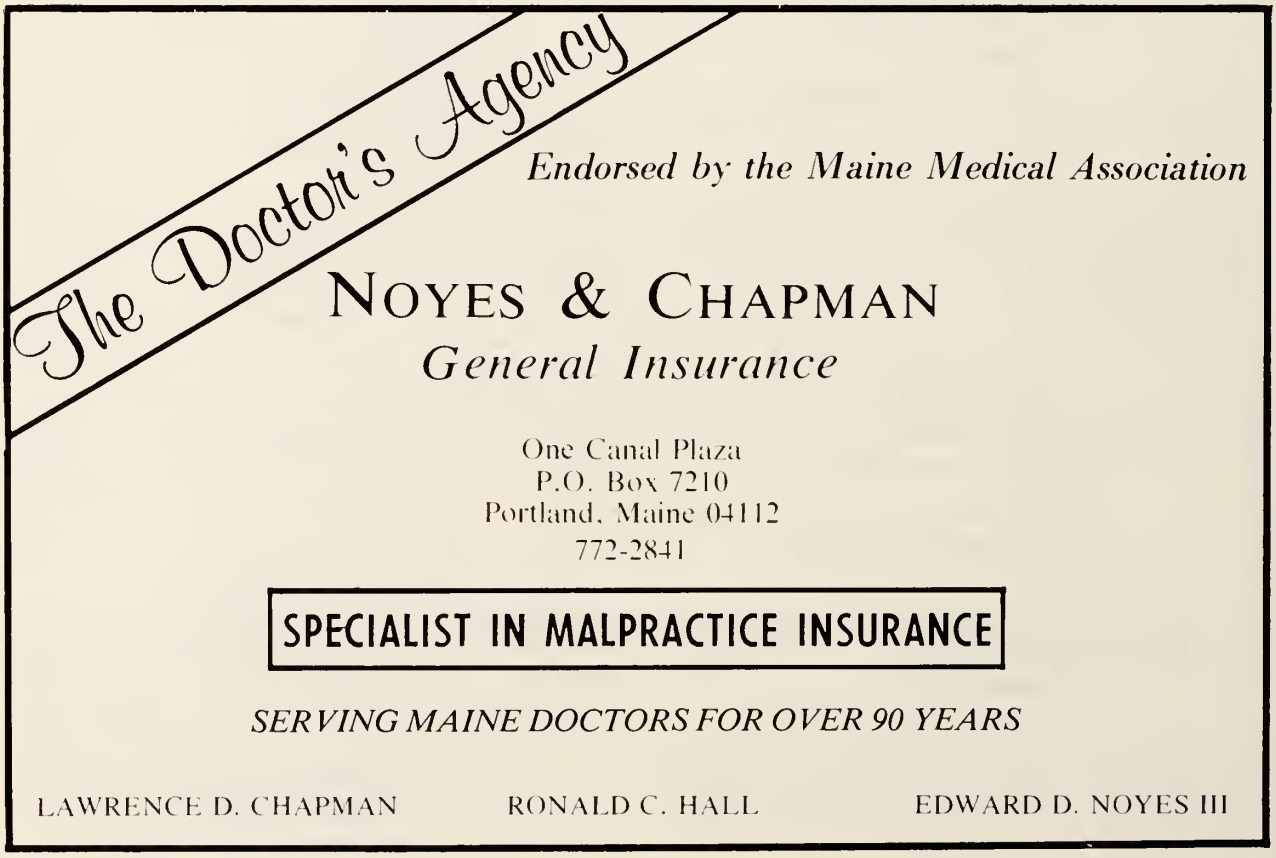
Henrietta D. Goodall Hospital
Sanford, Maine

Oct. 18, 1979 **"What's New in Oncology of the GI Tract"**
Michael Goldstein, M.D., Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts

The meeting will be held at the Henrietta D. Goodall Hospital's Conference Room. For further information contact Melvin Bacon, M.D.; 324-3632

Maine Medical Center
Portland, Maine

Every Mon.	Student Technologist Conference	8 a.m.
Every Mon.	Hematology Pathology Conference	11 a.m.
Every Mon.	Pulmonary Conference	12 Noon
Every Mon.	Pediatric Residents Conference	1 p.m.
Every Mon.	Anesthesia Formal Resident Lecture	3:30 p.m.
Every Mon.	Surgical Pathology Review	4 p.m.
Every Mon.	Radiology Journal Club	5 p.m.
1st & 3rd Mon.	Clinical Nephrology Conference	11 a.m.
1st & 3rd Mon.	Hematology-Pathology Conference	12 Noon
3rd Mon.	Eye Conference	11:45 a.m.
Every Tues.	Radiology Residents' Seminar	7 a.m.
Every Tues.	Family Practice Grand Rounds	9 a.m.
Every Tues.	Electrocardiographic Interpretation	1 p.m.
Every Tues.	Psychiatric Grand Rounds	1:30 p.m.
Every Tues.	Anesthesia Formal Resident Lecture	3:30 p.m.
Every Tues.	Surgical Seminar	4 p.m.
Every Tues.	Pathology Slide Seminar	4 p.m.
1st & 3rd Tues.	Radiology Pathology Conference	12 Noon
1st & 4th Tues.	Neurology Conference	12 Noon
2nd Tues.	Infectious Disease Conference	12 Noon
3rd Tues.	Hematology Conference	12 Noon
5th Tues.	Oncology Conference	12 Noon
Every Wed.	Radiation Therapy Conference	7 a.m.
Every Wed.	Urology Conference	7 a.m.
Every Wed.	Student Technologist Conference	8 a.m.
Every Wed.	Continuing Education Seminar	8 a.m.
Every Wed.	Medical Conference	9 a.m.
Every Wed.	Psychiatric Journal Club	12 Noon
Every Wed.	Cardiology Seminar	12 Noon
Every Wed.	Surgical Grand Rounds	5 p.m.
2nd Wed.	Guest Internist—Medical Conference	9 a.m.
4th Wed.	Medical Mortality Conference	9 a.m.
Alt. Wed.	Neurology-Psychiatry Seminar	11 a.m.
Alt. Wed.	Anesthesiology Journal Club	3 p.m.
Every Thurs.	Thoracic Surgery Conference	7 a.m.
Every Thurs.	OB/GYN Conference	7 a.m.
Every Thurs.	Anesthesiology Clinical Conference	7 a.m.
Every Thurs.	Diagnostic Radiology Teaching Conference	7 a.m.
Every Thurs.	Surgical Conference	8 a.m.
Every Thurs.	Pediatric Conference	9 a.m.
Every Thurs.	Tumor Consultation Board	11 a.m.
Every Thurs.	Medical Resident Conference	12 Noon
Every Thurs.	Surgical Seminar	4 p.m.
Every Thurs.	Endocrinology Conference	5 p.m.
Every Thurs.	Dental Specialty Lecture	6 p.m.
1st Thurs.	Anesthesia Mortality Conference	7 a.m.
1st Thurs.	Guest Pediatrician	9 a.m.
1st & 3rd Thurs.	Gastroenterology Conference	12 Noon



1st & 3rd Thurs.	Cardiac-Surgical Conference	12:30 p.m.
1st, 3rd, & 5th Thurs.	Pulmonary Physiology Conference	12:30 p.m.
2nd Thurs.	Cardiology Teaching Conference	12:30 p.m.
2nd Thurs.	Clinical Anesthesiology Lecture Series	3:30 p.m.
2nd Thurs.	Eye Staff Scientific Session	5:30 p.m.
2nd Thurs.	Maine Medical Center Medical Staff Meeting and Scientific Session	6 p.m.
2nd & 4th Thurs.	Pulmonary-Pathology Conference	12 Noon
2nd & 4th Thurs.	Endocrinology Conference	12 Noon
3rd Thurs.	Combined Guest Physician or Guest Surgeon Program	8 a.m.
3rd Thurs.	Clinical Anesthesiology Lecture Series	3:30 p.m.
4th Thurs.	Surgical Mortality Conference	8 a.m.
4th Thurs.	Anesthesia Mortality Conference	3:30 p.m.
Last Thurs.	Pediatric Mortality Conference	9 a.m.
Every Fri.	Thoracic Surgical Conference	7 a.m.
Every Fri.	Nuclear Medicine Conference	7 a.m.
Every Fri.	Student Technologist Conference	8 a.m.
Every Fri.	Neurological Neurosurgical Conference	8:30 a.m.
Every Fri.	Gastroenterology Conference	9 a.m.
Every Fri.	Medical Rehabilitation Staff Conf.	9 a.m.
Every Fri.	Orthopedic Conference	9 a.m.
1st Fri.	Dermatology Conference	12 Noon
2nd Fri.	Nephrology Conference	12 Noon
3rd Fri.	Rheumatology Conference	12 Noon
4th Fri.	Oncology Conference	12 Noon
Alt. Fri.	Oncology Radiation Conference	7 a.m.
Alt. Fri.	Gastroenterology Conference	10 a.m.

All programs have been certified AMA Category I. For further information contact Costas T. Lambrew, M.D.; 871-2111

Mercy Hospital
Portland, Maine

Oct. 2, 1979: 8-9 a.m.
Anesthesiology—Interoperative Intensive Care
Eric Polk, M.D., Mercy Hospital, Portland, Maine

Oct. 4, 1979: 7-8 p.m.
The Place of Estrogens
William F. Crowley, Jr., M.D., Massachusetts General Hospital

All programs have been certified AMA Category I. For further information contact Harold Pariser, M.D.; 774-1461, Ext. 363

Mid-Maine Medical Center
Waterville, Maine

Sept. 25, 1979: 12-1 p.m.
Analysis of Stillborns
Herbert A. Bartholomew, M.D., Augusta General Hospital
Paul A. Jones, M.D., Mid-Maine Medical Center

Oct. 16, 1979: 12-1 p.m.
Anemia and Pregnancy
Joseph J. Hiebel, M.D., MMMC

All programs have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621. Programs may be viewed over ITS.

V.A. Hospital
Togus, Maine

Oct. 1, 15, 22 2 p.m.
Educational General Staff Meetings
Topics to be announced

Oct. 9, 1979 12-1 p.m.
ITS Presentation
Topic to be announced

Oct. 3, 10, 17, 24, 31—1:15 p.m.
Educational Medical Staff Meetings
Topics to be announced

Programs have been certified AMA Category I. For further information contact E. Osborne Coates, Jr., M.D.; 623-8411

Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The Maine Medical Association's House of Delegates, at its June 1976 meeting, adopted a regulation stating that a *minimum of 150* hours of continuing medical education is required in order to maintain membership. The policy took effect on January 1, 1977 and all members must be certified by January 1, 1980. Eligibility for certification begins January 1, 1977.

Credits required for the three-year period are as follows:

Category 1 — CME Activities with Accredited Sponsorship **(60 hours required)**	**No limit**
Category 2 — CME Activities with Non-accredited Sponsorship	**45 hours**
Category 3 — Medical Teaching	**45 hours**
Category 4 — Papers, Publications, Book and Exhibits	**40 hours**
Category 5 — Non-supervised individual CME Activities	**45 hours**
Category 6 — Other Meritorious Learning Experience	**45 hours**

Only active, dues-paying members are required to report. Please fill in your activity report promptly and return to the M.M.A. office, P. O. Box 250, Brunswick, Maine 04011.

News, Notes And Announcements

1979-1980 Medical Education Program

The following is a brief outline of the 1979-1980 Medical Education Program for the Henrietta D. Goodall Hospital:

9/18/79	CAT Scanning
10/18/79	What's New in Tumors of the G.I. Tract
11/20/79	Advances in the Treatment of Diabetes Mellitus
12/20/79	Office ENT
1/22/80	Peripheral Vascular Disease
2/21/80	What's New in Endocrinology
3/18/80	Office GYN
4/17/80	Management of the Unconscious Patient
5/20/80	Drug Therapy 1980
6/19/80	Rectal Diseases

These programs will be certified accreditation for Category 1 of the AMA Physician's Recognition Award and for prescribed credits by the American Academy of Family Practice.

The Department of Postgraduate Medicine of Albany Medical College announces The Twentieth Anniversary Cruise January 4-16, 1980

The Albany Medical College has planned this Twentieth Anniversary Cruise as a very special event, combining twenty years of cruise experience with an outstanding faculty comprised of the chairmen of the Departments of Medicine, Psychiatry and Surgery, and the head of the Division of Cardiology. In addition to the formal presentations there will be many opportunities to discuss medical interests, person to person, with these experienced teachers. The shipboard postgraduate program is designed to interest all who have a part in patient care.

The education program is scheduled to allow participants the fullest advantage of the tax deductions permitted by the Internal Revenue Service.

This twelve-day cruise from New York (eleven days from Norfolk) will be aboard the luxurious Queen Elizabeth 2, "the greatest ship in the world." Ports of call include Curacao, Caracas, Grenada, Barbados and St. Thomas.

As an organization accredited for continuing medical education, the Albany Medical College of Union University certifies that this continuing medical education activity meets the criteria for 34.5 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association.

For information write to: Frank M. Woolsey, Jr., M.D., Department of Postgraduate Medicine, Albany Medical College, Albany, New York 12208.

The Medical College of Pennsylvania 3300 Henry Avenue Philadelphia, Pennsylvania 19129

Retraining Program for Clinically Inactive Physicians

When:	October 15-December 7, 1979 April 21-June 13, 1980
Where:	The Medical College of Pennsylvania
Purpose:	The Retraining Program is designed to facilitate the re-entry of clinically inactive physicians into clinical medicine through eight weeks of intensive clinical and didactic experience.
For Whom:	M.D.s and D.O.s who are either (1) totally inactive (no professional activity); (2) involved in non-clinical careers within the profession; or (3)

Continued on Page 373

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AVAILABLE ONLY ON PRESCRIPTION

Brief Summary

INDICATION: Tenuate and Tenuate Dospan are indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use such as those described below.

CONTRAINDICATIONS: Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result).

WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. *Drug Dependence*: Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy*: Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children*: Tenuate is not recommended for use in children under 12 years of age.

PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.

ADVERSE REACTIONS: *Cardiovascular*: Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System*: Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal*: Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic*: Urticaria, rash, ecchymosis, erythema. *Endocrine*: Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System*: Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous*: A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.

DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride): One 25 mg. tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg tablet daily, swallowed whole, in midmorning. Tenuate is not recommended for use in children under 12 years of age.

OVERDOSAGE: Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phentolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product Information as of April, 1976

MERRELL-NATIONAL LABORATORIES Inc.
Cayey, Puerto Rico 00633

Direct Medical Inquiries to
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Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215, U.S.A.

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References: 1. Citations available on request from Medical Research Department, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M.T., O'Dillon [Dillon], R.H., and Leyland, H.M.: A comprehensive review of diethylpropion hydrochloride. In: Central Mechanisms of Anorectic Drugs, S. Garattini and R. Samanin, Ed., New York, Raven Press, 1978, pp. 391-404.

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Complicated or not...

Tenuate® Dospan® (IV)

(diethylpropion hydrochloride NF)

75 mg. controlled-release tablets



A useful short-term adjunct in an indicated weight loss program.

Overweight patients in certain diagnostic categories often require strict appetite control and a successful program of weight reduction may tend to diminish the incidence or severity of the complications in some patients. Diethylpropion hydrochloride has been reported useful in such patients and while it is not suggested that Tenuate itself in any way reduces the complications of overweight, it may have a useful place as a short-term adjunct in a prescribed dietary regimen. **Tenuate should not be administered to patients with severe hypertension; see additional Warnings and Precautions on the opposite page.**

In uncomplicated overweight.

Many patients, on the other hand, present with excess fat but no disease. While this condition is often termed uncomplicated obesity, complications of both a social and a psychologic nature may be distressingly real for the patients. In these cases, a short-term regimen of Tenuate can help reinforce your dietary counsel during the important early weeks of an indicated weight loss program.

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The anorectic effectiveness of diethylpropion hydrochloride is well documented. No less than 16 separate double-blind, placebo-controlled studies attest to its usefulness in daily practice.[1] And the unique chemistry of Tenuate provides "...anorectic potency with minimal overt central nervous system or cardiovascular stimulation."[2] Compared with the amphetamines, diethylpropion has minimal potential for abuse.

Tenuate—it makes sense. And it's responsible medicine.

*Studies have shown that obesity is associated with an increased incidence of hypertension, symptomatic heart disease, adult-onset diabetes, and other diseases.

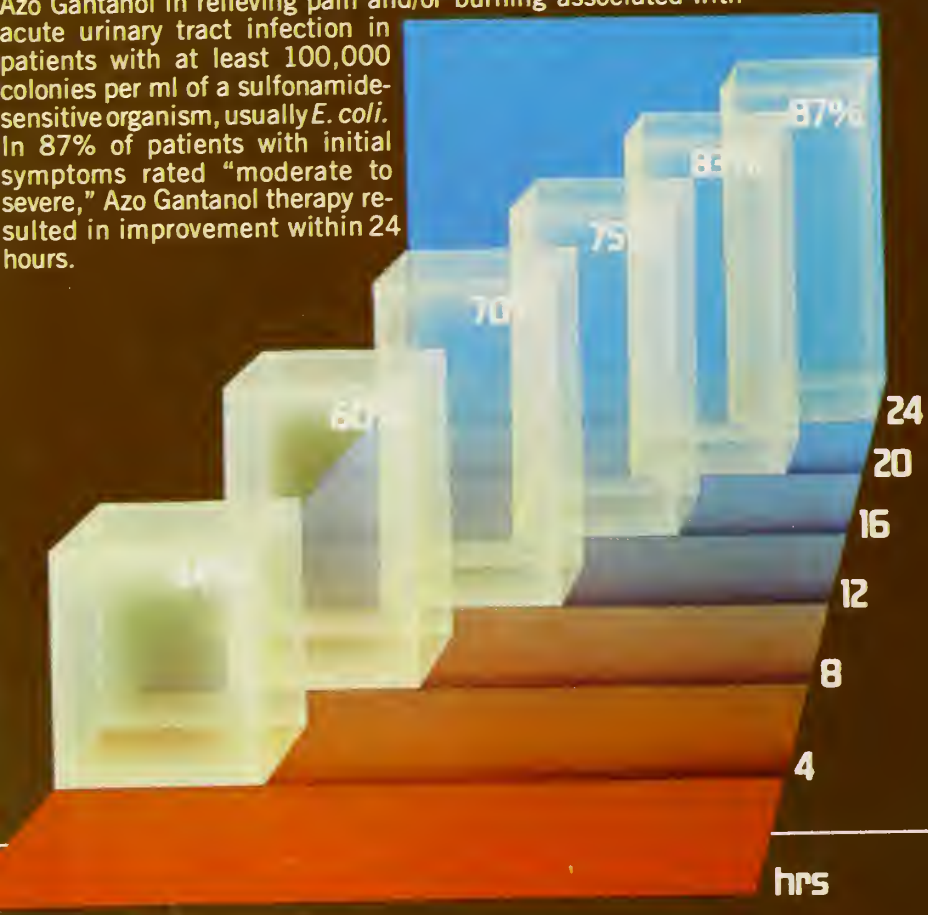
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For prescribing information see opposite page.

mportant data on the pain of acute cystitis:

In 87% of patients studied [303 of 349], Azo Gantanol® reduced pain and/or burning within 24 hours*

A controlled, multicenter study assessed the efficacy of Azo Gantanol in relieving pain and/or burning associated with acute urinary tract infection in patients with at least 100,000 colonies per ml of a sulfonamide-sensitive organism, usually *E. coli.* In 87% of patients with initial symptoms rated "moderate to severe," Azo Gantanol therapy resulted in improvement within 24 hours.



Before prescribing, please consult complete pro uct information, a summary of which follows:

Indications: In adults, urinary tract infections complicated by pain (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organis (usually *E. coli, Klebsiella-Aerobacter, Staphyl coccus aureus, Proteus mirabilis,* and, less fre quently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. **Note:** Ca fully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; a aminobenzoic acid to follow-up culture media. T increasing frequency of resistant organisms lim the usefulness of antibacterials including sul fonamides. Measure sulfonamide blood levels variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Children below age 12; sul fonamide hypersensitivity; pregnancy at term a during nursing period; because Azo Gantanol c tains phenazopyridine hydrochloride it is contr dicated in glomerulonephritis, severe hepatitis uremia, and pyelonephritis of pregnancy with disturbances.

Warnings: Safety during pregnancy not establi Deaths from hypersensitivity reactions, agranu tosis, aplastic anemia and other blood dyscras have been reported and early clinical signs (sor throat, fever, pallor, purpura or jaundice) may dicate serious blood disorders. Frequent CBC urinalysis with microscopic examination are re ommended during sulfonamide therapy.

Precautions: Use cautiously in patients with i paired renal or hepatic function, severe allerg bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria a stone formation.

Adverse Reactions: *Blood dyscrasias* (agran ulocytosis, aplastic anemia, thrombocytopeni leukopenia, hemolytic anemia, purpura, hypo thrombinemia and methemoglobinemia); *alle reactions* (erythema multiforme, skin eruption Stevens-Johnson syndrome, epidermal necrol urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbit edema, conjunctival and scleral injection, ph sensitization, arthralgia and allergic myocardi *G.I. reactions* (nausea, emesis, abdominal pa hepatitis, diarrhea, anorexia, pancreatitis an stomatitis); *CNS reactions* (headache, periph neuritis, mental depression, convulsions, ata hallucinations, tinnitus, vertigo and insomnia *miscellaneous reactions* (drug fever, chills, t nephrosis with oliguria and anuria, periarteriti nodosa and L. E. phenomenon). Due to certa chemical similarities with some goitrogens, d uretics (acetazolamide, thiazides) and oral h glycemic agents, sulfonamides have caused r instances of goiter production, diuresis and h glycemia. Cross-sensitivity with these agents exist.

Dosage: Azo Gantanol is intended for the ac painful phase of urinary tract infections. *Usu adult dosage:* 2 Gm (4 tabs) initially, then 1 (2 tabs) B.I.D. for up to 3 days. If pain persi causes other than infection should be sought After relief of pain has been obtained, contin treatment with Gantanol (sulfamethoxazole) be considered.

NOTE: Patients should be told that the oran dye (phenazopyridine HCl) will color the urin

Supplied: Tablets, red, film-coated, each co ing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 50

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for the pain

for the pathogens

anticipating career change to primary care fields from more specialized areas such as psychiatry, pathology, etc.

Format: Eight (8) weeks—Monday through Friday, 8AM until 5PM. Saturday and Sunday conferences optional.

Phase I : First three days of program are devoted to a basic review of medical history, physical examination and problem formulation. During this time participants take histories, perform physical examinations and review findings with assigned faculty.

Phase II: Mornings are devoted to small group tutorials and clinical rotations.

Didactic sessions conducted by MCP faculty are held every afternoon during the program. These consist of lectures and discussions which review current medical practice, generally by organ systems, and emphasize diagnosis and therapy.

Tuition: $1,950.00

Credit: This program is approved for AMA Category 1 Credit.

For application, write to Retraining Program for Inactive Physicians, Office of Medical Education, The Medical College of Pennsylvania, 3300 Henry Avenue, Philadelphia, Pennsylvania 19129

Basic Neurology for Psychiatrists and Generalists

March 3-7, 1980. Sponsor: University of Miami School of Medicine. Department of Neurology. Konover Hotel, Miami Beach, Florida. Course hours 30, AMA Category 1. INFORMATION: Division of Continuing Medical Education D23-3, University of Miami School of Medicine, P.O. Box 016960, Miami, Florida 33101. Tel. (305) 547-6716.

A Neurological Update

January 28-February 1, 1980. Sponsor: University of Miami School of Medicine, Department of Neurology. Americana of Bal Harbour, Miami Beach, Florida. Course hours 30, AMA, Category 1. INFORMATION: Division of Continuing Medical Education D23-3, University of Miami School of Medicine, P.O. Box 016960, Miami, Florida 33101. Tel. (305) 547-6716.

County Society Notes

York

The March meeting of the York County Medical Society was held on March 14, 1979 at Leedy's Restaurant, Alfred Square in Alfred. The program was as follows: Social Hour, 6:30 to 7:30 P.M., Dinner, Speaker and Business Meeting.

As has usually been the case in the past, a delicious dinner was served. Following this, two interesting presentations were made. The first was the progress report on the status of the Medical Mutual Insurance Company of Maine. The principal speaker was Dr. Jeremy R. Morton of Portland. Others who participated in this program included Dr. Richard Leck and members of the Board of Directors of this Insurance Company. The second speaker on the program was Dr. George McNeil, Jr. Director, Division of Community Psychiatry, Maine Medical Center, Portland. His subject was "Present Day Management of Depression." Both presentations were replete with questions and answers.

The business meeting was then called to order by our President, Dr. Connor M. Moore. The minutes of the annual meeting were dispensed with in the interest of time. There was no old business to report. As for new business, two items were presented. The first was the application of Dr. Alfred Hurwitz, a transfer from Kennebec County. He was unanimously accepted into our Society. The second item of importance was the discussion of a Resolution to be presented by Dr. Carl Richards from York County at the Annual Meeting of the House of Delegates. It concerned a letter from Senator Jay Kahn from Utah.

Now to present a couple of announcements:

1. The May meeting of the York County Medical Society will be held Wednesday, May 9, 1979 at the Webber Hospital, Biddeford, Maine. Committee in charge: Drs. Owen O. Dow, Roger J.P. Robert and Paul S. Hill, Jr.

2. The meeting of the House of Delegates will be held Saturday, April 7, 1979 at the Mid-Maine Medical Center in Waterville, Maine.

There was no correspondence of importance. However, there was one item that was presented under miscellaneous business. It was the opinion of all those present that all future County meetings be held away from hospital settings. However, the site of the next meeting on May 9, 1979 is to be held in the Biddeford area and will be left up to the discretion of the committee in charge. There were thirty (30) members and one (1) guest present.

The meeting was then declared adjourned.

MELVIN BACON, M.D., *Secretary*

Penobscot

The March meeting of the Penobscot County Medical Society was held at the Mary Jane Restaurant in Bangor on March 20, 1979. Fifty-two members attended including Dr. Alfred V. Persson, the featured speaker and Roland Larabee, a visiting medical student from the University of Vermont. After cocktails and dinner, the meeting was opened by the President, Dr. David S. Beebe and the minutes of the February meeting were approved without addition or change. The next order of business was the reading of two new applications for membership in the Society—one for regular membership by Dr. Geoffrey Gratwick, a rheumatologist practicing in Bangor, and the second for a junior membership by Dr. Bernard Price, a Family Practice resident at Eastern Maine Medical Center. Both applicants were elected to membership by written ballot. Dr. Beebe then discussed and outlined the forthcoming meeting of the House of Delegates of the Maine Medical Association. Dr. Robert J. Barrett, Jr. read a report on the formation of the resolutions committee and presented a resolution on the passing of Dr. Mason Trowbridge. A copy of the resolution is to become a permanent part of the record of the Penobscot County Medical Society and a copy is to be sent to Dr. Trowbridge's widow.

Further discussion included the strong possibility that further certificate of need legislation will be pushed in the Legislature this year and most probably will be monitored closely by the Maine Medical Association.

Dr. Don L. Maunz then introduced the guest speaker for the evening, Dr. Alfred V. Persson, of the Lahey Clinic and New England Deaconess Hospital, who spoke on vascular testing. There being no further business, the meeting was adjourned.

The April meeting of the Penobscot County Medical Society was held at The Hilton Restaurant in Bangor on April 17, 1979. Thirty-two members were present. The only officer present was Dr. James R. Curtis, the secretary of the Society. Dr. Lightbody brought two guests who were interested in hearing our featured speaker. After cocktails and dinner, the meeting was opened by Dr. Curtis and the minutes of the March meeting were approved without addition or change. Dr. Francis Kittredge then introduced our featured speaker, Cumberland County Society President, Dr. Clement A. Hiebert.

Dr. Hiebert gave a historical background on the decision to undertake a free second opinion program in Cumberland County

and reported on their experience of greater than seven months with the program. Out of the two thousand operations done during the period of time in question, 41 patients requested a second opinion. None of the surgeons rendering second opinions were requested to do so more than three times except for Dr. Hiebert. Initial statistics on the program indicated a 75% agreement either to operate or not to operate with a 25% difference of opinion.

The discussion which followed Dr. Hiebert's presentation was one of the most lively and interesting that I have witnessed in the past several years. It was unfortunate that only about half of our usual number was present. Because of the low turn out and absence of officers, it was felt that any definitive vote concerning the appropriateness of this program for our County should be considered at a future meeting.

Some of the points we should probably address include: 1) The legal liability of the person rendering second opinion, 2) How we would handle these statistics gathered from a trial of this program, 3) Should our program include other participating counties such as Cumberland County, 4) Should surgeons only, be entitled to a vote on this program, or should internists be involved, and 5) Should a similar program be considered for internists.

There being no further constructive business, the meeting was adjourned. Dr. Hiebert graciously refused our Society's offer to pay for his airfare and lodging while in Bangor.

JAMES R. CURTIS, M.D., *Secretary*

Aroostook

A regular meeting of the Aroostook County Medical Society was held at King Henry's Motor Inn in Caribou on March 28, 1979. The meeting was called to order by the Society's President, Dr. Arthur K. Carton, at 8:25 p.m., and the minutes of the last meeting on January 17, 1979 were read and accepted. Twenty-two active members were in attendance.

The following communications were conveyed to the members by the President:

1. A letter from John F. Ezzy, Executive Director of Valley Health Services, Inc., indicated that the corporation was working toward setting up a medical clinic in Madawaska in conjunction with the Northern Maine Medical Center. In order to comply with Federal guidelines, a letter of support from the A.C.M.S. was requested. It was decided that the President or Secretary should contact the Madawaska area physicians to see how they felt about the clinic and a decision as to whether or not to support the clinic would be made at the next meeting based on this survey.

2. An interim report of the Free Second Opinion Program in Cumberland County was forwarded to the Society by Dr. Arthur D. Pendleton. The program was set up on a six month trial basis from August to February and preliminary feedback shows it to have worked out well. The topic of second surgical opinions was discussed with no decisions made.

3. A letter was received from Dr. Craig Young indicating that he would like to attend an advanced seminar on Physician Negotiations in Danvers, Massachusetts, from May 31 to June 3 as a representative of the County Medical Society and requesting that the Society pay for expenses incurred. It was moved and seconded that the Society give Dr. Young a $100 grant as an incentive to attend this seminar on our behalf.

4. John Bielecki thanked the Society in writing for the $500 scholarship award that he received.

5. An application for the 1979 scholarship award was received from Dr. George Higgins on behalf of his daughter Kendra who attends Northwestern University. It was unanimously decided that the student grant be awarded to Kendra Higgins this year.

The Treasurer's report was read, moved and seconded and a copy is on file.

Mention was made of the successful dinner meeting with the State legislators at the Keddy's Motor Inn on February 3. Sentiment was expressed hoping that this could continue on an annual basis.

Dr. Harry Helfrich gave a brief report of the previous two meetings of the Executive Committee of the Maine Medical Association. He indicated that the BC/BS rates for physician's policies obtained through the M.M.A. would be increasing shortly. Plans for a new building to house the M.M.A.'s headquarters were again mentioned with a possible alternative of purchasing and renovating an old home in Augusta at a purchasing price of $67,000. It has not yet been decided whether this will be financed by a single $100 assessment from each member or by an increase in dues by $10 to $15 annually. Problems with the budget at the State level were mentioned and felt to be due to the lack of increase in dues over the past five years to meet the cost of living increase. Funds may be diverted to the general fund as an alternative to increasing dues.

A major portion of the meeting was taken up with discussions of the proposed amendments to the Constitution and Bylaws of the A.C.M.S. A copy of these suggested revisions was sent in advance to all members. As a quorum of the Society was not in attendance, these amendments will be voted on at the next meeting.

Finally, Dr. Harry Helfrich announced that he would be leaving the county to accept a position with Smith, Kline and French Laboratories in Philadelphia. A new Executive Committee member will have to be appointed at the next meeting in his place.

JANET M. PARKER, M.D., *Secretary Pro tem*

Kennebec

A meeting of the Kennebec County Medical Association was held at the Silent Woman Restaurant in Waterville on April 26, 1979 and was called to order by the President, Dr. Valentine J. Moore following a nice meal. Forty-eight members and one guest were in attendance.

Business:

Dr. Feagin reported on the doings of the Executive Committee.

Dr. Frank J. Twadelle resigned as an alternate delegate and was replaced by Dr. George I. Gould.

Dr. Moore then introduced the speaker, Dr. Robert Deane, Director of the ICU at Vermont Medical Center in Burlington who presented a very informative discussion of the adult respiratory distress syndrome which was welcomed by the members of the Association.

Sixty-five members and guests of the Kennebec County Medical Association attended the May meeting at the Waterville Country Club on May 18, 1979 which was primarily a social meeting. Prior to the meeting, the Council voted to extend affiliate memberships to Drs. Lee Richards and Joseph P. Senenky because of their respective disabilities and retirement from practice. The Council also voted to participate in the vacation fund in honor of Dr. Dan Hanley's many years of dedicated service to the Association. The Secretary was instructed to forward a check for that purpose.

The meeting was called to order by the President, Dr. Valentine J. Moore, who accepted the report of the Nominating Committee chaired by Dr. Barron. Nominations for the following year are as follows:

President: Dr. John W. Towne, Waterville
Vice President: Dr. Robert A. Stram, Augusta
Secretary-Treasurer: Dr. O. Thomas Feagin, Augusta
Council: Drs. Gareth O.M. Jones and Neil A. Newton, both of Augusta, and Albert J. Pepe, Waterville

There was a motion for the Secretary to cast one ballot and this was so done.

Dr. John Towne introduced the Glowtones, a barbershop quartet from Waterville who delivered us a 30 minute program of barbershop music which was very entertaining. Following this, a group of musicians played for the dancing enjoyment of the members and a good time was had by all.

O. THOMAS FEAGIN, M.D., *Secretary*

Androscoggin

The meeting of the Androscoggin County Medical Association was held on May 17, 1979 at Chase Hall, Bates College in Lewiston. The meeting was called to order at 8:20 p.m. by the President, Dr. Lawrence A. Nadeau.

The minutes of the April 19 meeting were read and accepted.

Dr. Ake Akerberg read a Eulogy for a member of the County Society, Dr. Najib Pandya, who died on April 29, 1979. A moment of silence was observed. It was resolved that the Eulogy be adopted and made part of the Society's records and that a copy be sent to

his family.

Two items of correspondence were read by the Secretary. The first was a letter from Paul A. Cote, Esq. addressed to Jack Simmons, Esq., a copy of which had been sent to Dr. Nadeau. The letter concerned a proposed joint meeting between Lewiston-Auburn lawyers and doctors. Dr. Leo E. Cousineau, Vice-President, is working towards arranging this meeting in October. The second letter was from Beverley Heath, the Director of Welfare, City of Lewiston. She requested participation of the County Society in matters relating to prescrption drugs for welfare patients. The matter was referred to the Advisory Committee.

Two membership applications had been received and approved by the Credentials Committee. These were from Drs. David Eitel and Lawrence Hopperstead. These two physicians were unanimously voted to membership.

Dr. Gilbert R. Grimes then reported on the matters discussed by the M.M.A. Executive Committee. These largely had to do with the move of the M.M.A. headquarters from Brunswick to Augusta. An Augusta office has not yet been found, but the M.M.A. should soon be located in the Capital. A report on the House of Delegates meeting in Waterville was related by Dr. Grimes since that meeting had largely dealt with the matters of the proposed construction of a new headquarters at the Augusta Civic Center. It was decided by the House of Delegates not to proceed with the building as planned and furthermore to sell the plot of land at the Civic Center and seek a modest location in the Augusta area.

Drs. Thomas Shields and Cousineau then introduced the following **RESOLUTION** —

WHEREAS it is desirable for the Maine Medical Association to have the best group health insurance program possible at a reasonable price.

BE IT RESOLVED by the Maine Medical Association that it seek competitive bids for group health insurance for its members, their families, and their employees, at their earliest practical time.

This resolution was passed unanimously as a motion and will be presented to the House of Delegates meeting at Rockland in June.

Several announcements were made by the President, Dr. Nadeau:

1. He reported that flowers had been sent to Dr. Pandya's funeral service and that a memorial donation had been sent to the Tri-County Mental Health Services ($100.00).

2. He mentioned that members in the Maine Medical Association as of January 1, 1980 will require a certain number of credit hours over a three-year period.

3. Approximately 20 physicians are actively practicing in the Androscoggin County area who are not members of the County Society. The membership was urged to contact these individuals and encourage their joining the Society.

4. Dr. Nadeau mentioned that 14 members had not yet paid their County Society dues and that 20 members had not yet paid their $20.00 for the increase of the County Society dues.

Under new business, the mention was made of Dr. Hanley's upcoming retirement in June 1979. Dr. John A. James made a motion that the Androscoggin County Medical Association send a contribution of $5.00 per active member, the funds to be taken from the Society's Treasury. This motion was seconded by Dr. Daniel Shields and was passed; accordingly a check will be made out to the Hanley Fund.

Dr. Thomas Shields mentioned that the room in the Bates College Infirmary had been prepared for our use and that a desk and four chairs had been placed in the room as well. Dr. Fakhery then moved that a letter of appreciation be sent to the President of Bates College expressing gratitude that the College had made this space available to the County Society. This motion was passed unanimously and the Secretary will draft a letter.

There being no further business, the meeting was adjourned at 10:00 p.m.

EDWARD Z. WALWORTH, M.D., *Secretary*

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Letter To The Editor

To the Editor:

Re: "Unusually Long Survival of Patients With Cancer"
Loring W. Pratt, M.D.
Journal of the Maine Medical Association, February 1978

The day that the Maine Medical Journal appeared on my desk, I received word from a hospital in Florida that Patient #2 in this series had died. He had died of extensive metastatic carcinoma, thought to be small cell (oat cell) type, probably derived from lung or pancreas.

This then, represents a patient who has been seen and followed closely for eight years without evidence of recurrent tumor, but recurrent episodes of malignancy repeatedly during this time.

His final event was widespread carcinomatosis.

LORING W. PRATT, M.D.
37 Lawrence Avenue
Fairfield, Maine 04937

PREOPERATIVE TRANSFEMORAL CATHETER EMBOLIZATION OF HEAD AND NECK TUMORS

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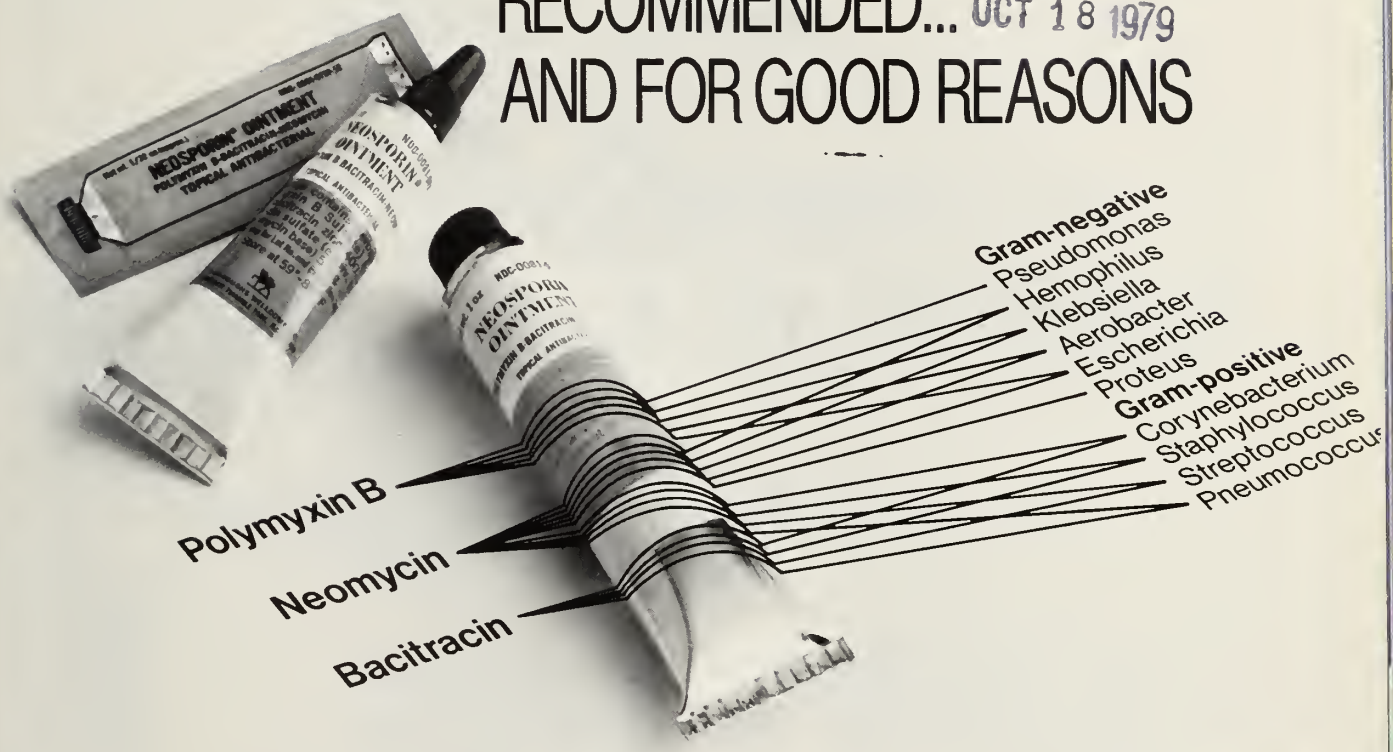
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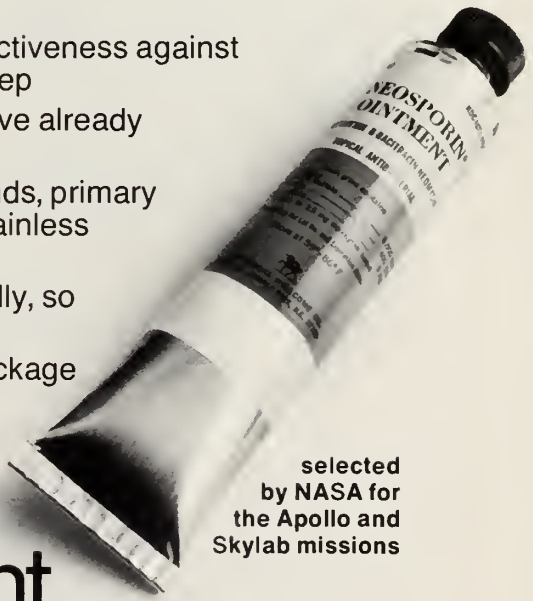
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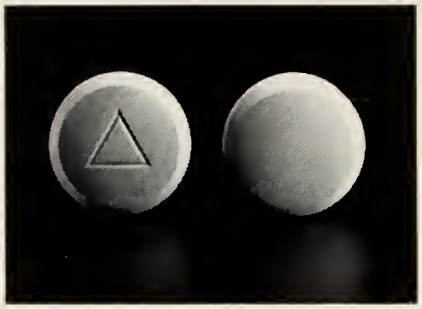
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Examining a Few Myths About Prescribing.



Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand-name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to a reference product. As y know, there is substan literature on this subje affecting many drugs, cluding such antibioti as tetracycline and ery thromycin. The record drug recalls and court actions affirms strong that there are differen among pharmaceutic companies and their products. Research-intensive companies have far better record than those that do no search and may pract minimum quality ass ance.

MYTH: Industry favors only "expensive" brand names and denigrates generics.

FACT: PMA compani make 90 to 95 percen the drug supply, inclu ing, therefore, most g generics. Drug nome clature is not the imp tant point; it's the co tence of the manufac turer and the integri the product that cou

Matters.

MYTH: Generic options almost always exist.

FACT: About 55 percent of prescription drug expenditure is for single-source drugs. This means, of course, that for only 45 percent of such expenditure, is a generic prescribing option available.

MYTH: Generic prescriptions are filled with inexpensive generics, thus saving consumers large sums of money.

FACT: Market data show that you invariably prescribe—and pharmacists dispense—both brand and generically labeled products from known and trusted sources, in the best interest of patients. In most cases the patient receives a proven brand product. Savings from voluntary or mandated generic prescribing are grossly exaggerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

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The Journal
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Percutaneous Transthoracic Needle Biopsy

J. Mark Kjeldgaard, M.D.*

Abstract

Percutaneous transthoracic needle biopsy is an accurate, well tolerated procedure for the diagnosis of a solitary pulmonary nodule or localized pulmonary infiltrate. This paper describes the first 15 consecutive cases using the Rotex Biopsy instrument. The diagnosis was made in all fifteen; fourteen malignancies and one Nocardia asteroides. The only complication was pneumothorax in four, three of whom required a chest tube. This technique is particularly useful in establishing a diagnosis in the high risk patient with a new peripheral nodule or in the compromised host.

Evaluation of a pulmonary nodule or localized pulmonary infiltrate is a common pulmonary problem. Often it is desirable to establish a diagnosis without the risk of a thoracotomy or before proceding with a thoracotomy in a high risk patient. A percutaneous transthoracic needle biopsy is a safe, well tolerated procedure with a high diagnostic yield.[1] Of the variety of techniques which have been developed to obtain tissue transthoracically, the most common is the aspiration needle biopsy with an 18-22 gauge needle inserted into the lesion under fluoroscopic guidance.[2,3,4,5,6] Various modifications of the needle instrument have been designed to improve diagnostic accuracy.[7,8,9] The pulmonary group at the Maine Medical Center has recently changed to the Rotex biopsy instrument as described by Nordenström because the material obtained appears superior to the aspiration biopsy.[10,11] It is safe, well tolerated and has minimal complications. This paper describes the first 15 cases since changing from the aspiration technique.

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Procedure

The Rotex biopsy instrument consists of a stainless steel screw 220 mm long and 0.55 mm in diameter and a thin walled 1.0 mm stainless steel cannula 160 mm long. A special needle holder stabilizes the needle, denotes the screw location within the cannula and allows the operator to keep his hand out of the direct line of the x-ray beam.

The patient is NPO for 4 hours before the procedure and is given no pre-medication unless there is excessive anxiety. Either the supine or prone position is used depending upon the anterior-posterior location of the lesion. Utilizing biplane fluoroscopy, the lesion is localized in two planes. Following local anesthesia, the Rotex biopsy instrument is passed aseptically into the lesion while checking needle position in both planes. The screw needle is rotated clockwise through the lesion for a distance of 1.5 cm. The cannula is then advanced counterclockwise to the same depth to enclose the needle and protect the specimen. This takes the core of cells from the periphery of the lesion minimizing the possibility of obtaining necrotic debris from the center of a tumor.

The instrument is then withdrawn and the needle handed to a cytology technician who prepares slides immediately for cytologic evaluation using the Papanicolaou technique. The needle can be placed directly into culture medium or the specimen can be smeared for special stains such as TB or fungus. If a lymphoma is suspected, several air dried smears should be made for staining. The patient is then fluoroscoped to ensure there is no immediate pneumothorax and a followup expiratory PA roentgenogram is obtained to look for a pneumothorax. If the procedure is performed on an outpatient, the patient is observed 4 hours after the procedure and then carefully instructed about the symptoms of a pneumothorax and urged to return to the hospital should these symptoms develop.

Representative Cases and Data

Case 1: A 50-year-old male was referred for evaluation of a 1.5

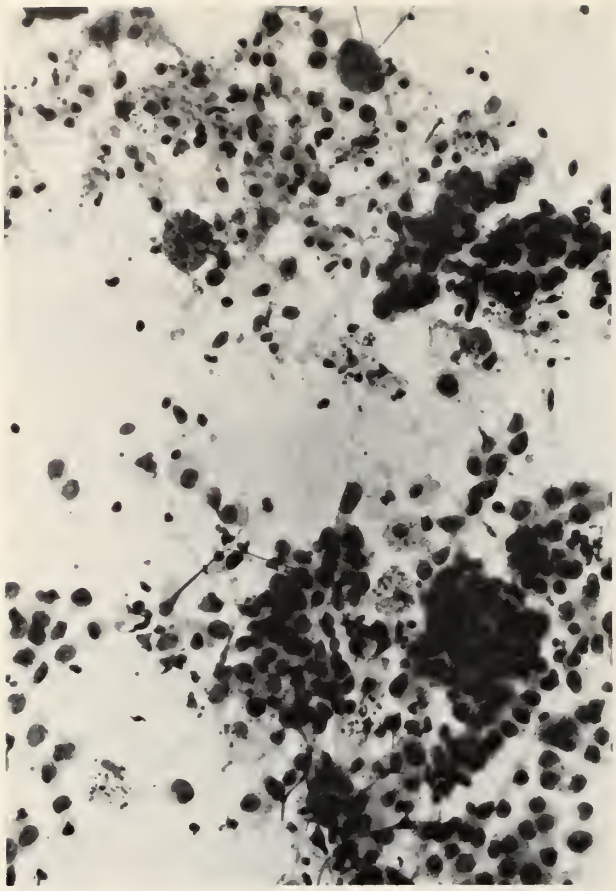


Fig. 1. The above photograph reveals abundant cellularity with well defined nuclear features of malignancy. The lack of organization suggests an undifferentiated carcinoma, large cell type.

cm x 1.5 cm solitary pulmonary nodule located in the superior segment of the right upper lobe. He had a 70 pack year history of cigarette smoking and pulmonary function studies indicated such severe airway obstruction that he was not a surgical candidate. His chest roentgenogram revealed bullous emphysema and a non-calcified 1.5 cm nodule in the right lower lobe. Needle biopsy was positive for large cell undifferentiated carcinoma of the lung (see Figure 1). The patient was referred to Radiation Therapy by his primary physician.

Case 2: A 55-year-old male with poorly differentiated nodular lymphoma was found to have a right upper lobe pulmonary nodule and cryptococcal meningitis. The meningitis improved with Amphotericin B and 5-Fluorocytosine; however, the right upper lobe lesion continued to enlarge and several smaller lesions were observed. Needle biopsy revealed branching acid-fast hyphae and culture grew out Nocardia asteroides. He was treated with sulfisoxazole and minocycline.

Diagnosis was achieved with the Rotex biopsy instrument in all of the first 15 patients. Nine of the patients were male; all except one had cancer. Large cell undifferentiated was the most common cancer (7 patients) followed by adenocarcinoma (4 patients). All except one were felt to be primary lung tumors. Four patients developed pneumothorax (26%) and three of these required a chest tube for 12 hours (20%). These complication rates are comparable to those reported in the literature for other series. No other complications were observed.

Comments

Percutaneous transthoracic needle biopsy is an accurate method of diagnosing peripheral nodules or

Continued on Page 385

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Table 1

Age	Sex	Indication	Diagnosis	Complication
66	M	S.P.N.*	keratinizing squamous cell	None
70	M	S.P.N.	adenocarcinoma	None
83	M	S.P.N.	adenocarcinoma	pneumothorax—chest tube
57	M	S.P.N.	large cell undifferentiated	None
74	F	S.P.N.	anaplastic (CA)	None
65	F	S.P.N.	adenocarcinoma	None
76	M	S.P.N.	undifferentiated	None
63	F	S.P.N.	adenocarcinoma	pneumothorax—chest tube
70	F	S.P.N.	large cell undifferentiated	None
73	M	S.P.N.	large cell undifferentiated	None
55	M	Multiple pulmonary nodules	Nocardia asteroides	10% pneumothorax—no chest tube
52	F	Left apical mass	large cell undifferentiated	None
50	M	S.P.N.	large cell undifferentiated	None
57	M	3 x 3 cm peripheral nodule	large cell undifferentiated	None
62	F	2 x 2 cm coin lesion	large cell undifferentiated	pneumothorax—chest tube

*S.P.N. = solitary pulmonary nodule

infiltrates. This approach has been found in several series to be more accurate than bronchoscopy even when the latter is performed under fluoroscopy with brush biopsy or transbronchial lung biopsy.[1,2,4] Our experience would confirm this finding. There is little or no pain and only a few minutes are required once the lesion has been located fluoroscopically. The major complication is pneumothorax which will often respond to observation and oxygen alone; otherwise responding easily to chest tube drainage. A new technique has been described using a plastic catheter as an introducer for the biopsy instrument and homologous blood as a seal and reportedly will reduce the risk of a pneumothorax to less than 10 percent.[8,12] This technique will be investigated in our own institution with further biopsies. Other risks include minor hemoptysis and rarely a hemothorax. We have not seen this complication yet and others report no major pulmonary hemorrhage.

Needle biopsy need not compete with other diagnostic techniques nor is it the goal of this paper to advocate it for all peripheral lesions. However, transthoracic needle biopsy is a valuable diagnostic technique in the following circumstances;

1) *The patient with metastatic disease* It allows rapid evaluation of a pulmonary lesion in a patient who presents with symptoms of metastatic disease to the brain or bone but no tissue diagnosis is available. A diagnosis can often be obtained rapidly and radiation therapy and/or chemotherapy begun.
2) *High risk patient* Patients with significant pulmonary or cardiovascular disease may be at high risk for a thoracotomy and pulmonary resection. Approximately 40-50% of solitary pulmonary nodules prove to be malignant, and if a diagnosis of cancer can be established preoperatively, a thoracotomy may be undertaken in the high risk patient. A negative biopsy for cancer is not conclusive, but may persuade the physician to observe the lesion and its biologic behavior in the high risk patient. There are also situations where the patient is reluctant to have surgery but will accept a thoracotomy once the diagnosis of cancer has been made. For these patients, a needle biopsy preoperatively would be useful.
3) *Pancoast tumor* A tissue diagnosis may be difficult to obtain in the patient with a superior sulcus tumor (Pancoast tumor).[13] Transthoracic needle biopsy is reported to have a high diagnostic yield and should be considered as soon as it is apparent that sputum cytology is negative.
4) *The compromised host* The patient who is a compromised host because of chemotherapy or immunotherapy often presents with a peripheral pulmonary mass or infiltrate. It is virtually im-

possible to tell from the roentgenographic appearance whether this represents a neoplasm or some form of infection. In the small peripheral lesion, a needle biopsy will often allow rapid identification of the organism or tumor and treatment can be begun with minimal delay.

It is always difficult to know what to do when the transthoracic needle biopsy report comes back nondiagnostic and negative for malignancy. One cannot put complete reliance in any technique short of complete resection of the lesion; a biopsy which is negative should have a second needle biopsy, another type of diagnostic procedure or close observation with frequent chest roentgenograms.

Biplane fluoroscopy was used on all needle biopsies in this series and may have contributed to high yield of positive diagnosis in spite of lesions less than 2 cm in diameter. Single plane fluoroscopy is adequate for larger peripheral lesions but biplane fluoroscopy will make the procedure faster. In addition to good fluoroscopy, a second essential feature for a successful transthoracic needle biopsy is an experienced cytologist. The specimens are prepared using the Papanicolaou technique and require skill in preparing the specimen and experience in interpretation. Care must be taken to exclude patients with a bleeding diathesis and there is a higher risk of pneumothorax in patients with pulmonary emphysema.

Percutaneous transthoracic needle biopsy is an accurate, well tolerated, safe, diagnostic technique useful in the evaluation of peripheral pulmonary nodules or infiltrates.

Acknowledgements

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Reminder to M.M.A. Members

CONTINUING MEDICAL EDUCATION ACTIVITY REPORT

The Maine Medical Association's House of Delegates, at its June 1976 meeting, adopted a regulation stating that a *minimum of 150* hours of continuing medical education is required in order to maintain membership. The policy took effect on January 1, 1977 and all members must be certified by January 1, 1980. Eligibility for certification begins January 1, 1977.

Credits required for the three-year period are as follows:

Category 1 — CME Activities with Accredited Sponsorship **(60 hours required)**	**No limit**
Category 2 — CME Activities with Non-accredited Sponsorship	**45 hours**
Category 3 — Medical Teaching	**45 hours**
Category 4 — Papers, Publications, Book and Exhibits	**40 hours**
Category 5 — Non-supervised individual CME Activities	**45 hours**
Category 6 — Other Meritorious Learning Experience	**45 hours**

Only active, dues-paying members are required to report. Please fill in your activity report promptly and return to the M.M.A. office, 524 Western Avenue, Augusta, Maine 04330.

The Medical Management of the Patient With Recurrent Affective Disorder

WALTER R. CHRISTIE, M.D. AND THOMAS W. SAMUELSEN, M.D.*

Rational medical management of affective disorders depends on rational diagnosis. Criteria for psychiatric diagnosis have often been vague, and the syndromic pattern of any given psychiatric disorder has been left to the wisdom of differing schools of psychiatric thought. Today, however, in an era of increased treatment specificity, accurate diagnosis of the mentally ill patient has a new urgency.[1]

This is the second of two papers focusing on the treatment of patients with recurrent, endogenous mood disorders. In the first (October 1977), the authors stressed the psychological strategies helpful with these patients. This paper discusses the importance of objective, descriptive diagnosis and the techniques of medical management.

Almost a century ago, Emil Kraepelin gave excellent descriptions of both typical and atypical forms of affective disorders.[2] A knowledge of his contribution is still important to today's clinician. More modern criteria, such as those laid forth by Spitzer and Endicott in *Research Diagnostic Criteria*, provide clear definition.[3] There also exist sensitive rating scales, such as the Severity of Depression and Mania scale, the Zung Scale for Depression, the Hamilton Scale for Depression and the Manic Behavior Rating Scale, which provide both quantitative and qualitative information.[4] A problem in psychiatric diagnosis is that some signs and symptoms may overlap into the constellation of another disorder. For example, both manics and depressives may suffer from hallucinations and delusions and on the basis of these be diagnosed as schizophrenics. Distorted patterns of speech and thought, common in mania, may also evoke a diagnosis of schizophrenia. Psychotic withdrawal and muteness, not uncommon in the severest depressions, must be carefully distinguished from catatonia and toxic organic brain syndromes. The lability, manipulativeness, referentiality, dependency, irritability and poor social integration common in many mood-disordered patients must be differentiated from organic, neurotic and characterological states. Mood disorders produce a varied symptomatology that can lead to misdiagnosis. Today we have drugs available which are specific for mood disorder, and since a mood disorder can only be rationally treated by specific medications when there is a clear understanding of the general phenomenology of the illness, accurate diagnosis of affective disorders is crucial.

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CHEMOTHERAPY IN MANIC-DEPRESSIVE PATIENTS

For the management of mood disorder, we have three groups of drugs, two of which are specific and one which is non-specific.

I. Lithium Carbonate—anti-manic agent of first choice
II. Anti-depressants
  A. Tricyclics—first choice in depression
  B. Monoamine oxidase inhibitors—alternative choice in depression
  C. Lithium Carbonate—alternative in depression
III. Neuroleptics—nonspecific calming agents in mania or depression.

I. Lithium Carbonate as an Anti-manic Agent

This agent has not yet unlocked all of its secrets to us. Since 1949, it has been used in mania and in that condition has been more successful than any other medicine.[5] When lithium is used in mania, one does not hope that the patient will improve; rather one expects that he will. When the drug does fail, it is usually because toxic effects precede or are congruent with a therapeutic dose. Is the lithium ion safe? The answer must balance benefit against risk. Many manics would be doomed to a lifetime of illness were it not for lithium. Lithium's use in the manic population has been responsible for a return to productive social and economic functioning. The gain-risk ratio is strongly on the gain side. Yet its potential toxic effects are such that its use requires considerable judgement. The lithium ion is highly active and mobile. It diffuses itself into all body fluids, competing with sodium and potassium ions. Toxic effects cannot always be correlated with either substance weight ingested or with serum mEq levels. Age is an important factor in the tolerance of lithium. The half-life of the lithium ion is 18 hours in younger people and 36 hours in older people.[6] Considerably higher mEq levels are encountered in the aging population on doses that would not produce such levels in a younger population. Although manics in their late fifties and older can usually be managed smoothly with lithium carbonate, they may be somewhat more "brittle" than the younger population. Persons in the higher age group often develop levels of 1.0 or more mEq's on less than gram doses of lithium daily.

A special problem is the treatment of those manics who do not respond until lithium reaches a level where toxicity becomes apparent. Thus it is useful to remember there are no magic serum lithium levels which define efficacy on the one hand and toxicity on the other. Nonetheless, therapeutic levels are con-

sidered overall to lie in the range of 0.5 to 1.6 mEq's.[7] We believe the latter figure represents an outside limit. We treated one patient who for a period of time was able to carry levels of close to 2.0 mEq's with benefit to her mixed mood state. Within weeks neurotoxicity, manifested by lethargy, slurred speech, and generalized tremor, dictated a reduction of lithium. However, at the lower level her mood disorder became more apparent.

Lithium Toxicity

Literature on this topic is large and ever-expanding. It is not known whether lasting toxicity is related to length of use alone, is idiosyncratic, or is related to a combination of high dose and long-term use. For practical purposes, we accept the following: lithium carbonate at high mEq levels or high daily gram levels does cause troubling side effects. We find it convenient to consider these effects in the following clusters:

1. Cerebellar: There may be a fine-intention tremor of the fingers or a coarse, generalized shaking of the hands and other body parts. Coordination may be very poor, as evidenced by dysdiadochokinesis, ataxia, and dysmetria.

2. Cortical: Mild confusional states or frank delirium with visual hallucinations or illusions may be prominent. Care is required not to confuse this iatrogenic effect with the illness itself.

3. Neuro-muscular: Reduced to absent d.t.r.'s, possible pendulous knee jerks are encountered. Fasciculations may be felt in the extremities, occurring spontaneously or elicited by tapping major muscle masses.

4. (?) Hypothalamic: *Weight gain* is due to an increased desire for candy, carbohydrates, and sweet drinks. Obesity can be a health-threatening problem in certain patients. All too often lithium therapy is associated with obesity. Lithium *thirst*, which should be differentiated from the extra intake induced by dry mouth, is a deep thirst. We consider the induced polydipsea as *mild* when less than 1.5 liters of extra fluid are needed, *moderate* when 1.5 to 3 liters of extra fluid are needed, and *severe* when more than 3 extra liters are ingested.

5. (?) Hypothalamic-renal: Diuresis is measured as above. Interestingly, patients who give a history of greatly increased fluid intake do not always give a corresponding history of excess urination, nor do they complain as much about the increased urine output as they do about the thirst. A question under intensive investigation today is the potential of the lithium ion to damage the kidney in the interstitium and nephron.[8,9,10]

6. Thyroid: Not uncommonly, patients undergoing lithium therapy develop a soft, usually uniformly enlarged thyroid. Although a euthryoid state may persist, clinical hypothyroidism is not uncommon. A high index of suspicion for lithium-induced hypothyroidism is important, since hypothyroidism itself can induce depression; and here again, there is a danger of confusing an iatrogenic state with the illness under treatment. In working with lithium patients, one must have a close cooperative relationship with an endocrinologist in order that the patient's clinical state, TSH levels, and Free T4 levels may be appropriately evaluated.

7. Lethargy: A generalized subjective tiredness and objective muscle weakness may result from lithium. The former is more prevalent than the latter.

8. Gastrointestinal disturbances: These are usual only when lithium therapy must be initiated in gram doses. They are seldom a problem when lithium can be given in gradually increasing doses up to a therapeutic level. Giving lithium with meals is also ameliorating. The G.I. disturbances include nausea and vomiting, loose bowels, and diarrhea.

To properly manage a patient on lithium, the physician should consider the side effects mentioned above at each visit.

How much lithium should be given to the mood-disturbed patient? One should give as little as possible commensurate with control of the mood disorder. If a patient is functioning well in personal and economic life, all the while being slightly hypomanic, it is probably just as well to assume that he is properly regulated. Indeed, some slightly hypomanic patients do better in that state overall than in any other.

How often should plasma lithium determinations be done? The patient undergoing stabilization should be monitored on a daily or every-other-day basis until levels are stable and the patient's mood is satisfactory. Levels on a weekly basis are then possible. When the patient is functioning in his normal milieu, only monthly or even trimonthly levels are required. However, lithium toxicity should not be judged by mEq levels; rather the toxic symptoms mentioned above are the principal criteria for lithium toxicity.

II. Antidepressants

A. Tricyclics

We generally institute tricyclic therapy with imipramine because it shares properties found in all members of the tricyclic group. It is moderately anticholinergic and initially often moderately sedating, although on occasion it may be stimulating. If, for instance, a patient has a moderate depression, one in which social and personal functioning in a non-hospital setting is possible, we begin typically with 75 mgs. of imipramine about an hour before bedtime.

We carefully inform the patient about possible side effects. We say that side effects are variable and that most of them largely wear off. We explain that a "medicated" feeling is possible for up to a week but that it generally subsides within four or five days. Next we describe the nature of orthostatic hypotension and say that this is also usually only an initial effect which, however, should be guarded against by not shifting position too suddenly and by not arising from bed too vigorously, especially in the dark. Intermittent sweats and some constipation are possible, and dryness of the mouth will probably occur; in-

Continued on Page 390



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...in the functional bowel/irritable bowel syndrome*

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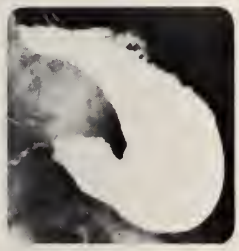
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helps control abnormal motor activity
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Demonstrated smooth muscle relaxant activity.

In this double-blind study, twenty patients having G.I. series and exhibiting spasm were randomly selected to receive either 2 cc. of Bentyl or sodium chloride intramuscularly. Ten minutes after the injection another radiograph was taken . . .

. . . Bentyl produced definite relaxation in 8 of 10 patients. The sodium chloride produced relaxation in only 3 of 10. No side effects occurred in either group of patients.



Pylorospasm has almost totally blocked passage of barium meal.



Barium meal beginning to pass 10 minutes after intramuscular injection of 20 mg. Bentyl.

"The correlation of spasm relief and drug given was excellent."

*This drug has been classified "probably" effective in treating functional bowel/irritable bowel syndrome.

†See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964.

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Brief Summary

INDICATIONS

Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the following indications as "probably" effective:

For the treatment of functional bowel/irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

THESE FUNCTIONAL DISORDERS ARE OFTEN RELIEVED BY VARYING COMBINATIONS OF SEDATIVE, REASSURANCE, PHYSICIAN INTEREST, AMELIORATION OF ENVIRONMENTAL FACTORS.

For use in the treatment of infant colic (syrup).

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient; unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: Autonomic neuropathy. Hepatic or renal disease. Ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension. Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia; urinary hesitancy and retention; blurred vision and tachycardia; palpitations; mydriasis; cycloplegia; increased ocular tension; loss of taste, headache; nervousness; drowsiness; weakness, dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling, severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs.

Usual Dosage: Bentyl 10 mg. capsule and syrup: *Adults*: 1 or 2 capsules or teaspoonfuls syrup three or four times daily. *Children:* 1 capsule or teaspoonful syrup three or four times daily. *Infants*: ½ teaspoonful syrup three or four times daily. (May be diluted with equal volume of water.) Bentyl 20 mg.: *Adults*: 1 tablet three or four times daily. Bentyl Injection: *Adults*: 2 ml. (20 mg.) every four to six hours intramuscularly only. NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE: The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

Product Information as of October, 1978.

Injectable dosage forms manufactured by CONNAUGHT LABORATORIES, INC., Swiftwater, Pennsylvania 18370 or TAYLOR PHARMACAL COMPANY, Decatur, Illinois 62525 for MERRELL-NATIONAL LABORATORIES, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215, U.S.A.

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deed, dry mouth is generally the most ongoing side effect. When the patient is a middleaged male, urinary hesitancy is not uncommon, and the patient is informed about this. Should problems or concerns arise, the patient is requested to call us any time over the week until he is seen again. A one-week supply of medication is prescribed.

When the patient is seen again in a week's time, a formal or informal rating of mood status is performed. Unless response is rated very good, dosage is generally increased at this time to 100 mgs., usually at h.s. The same contact and appointment plan is followed. The drug is now either kept at that dosage or, more usually, raised to 150 mg. per day. Splitting the dose does not usually have any positive or adverse effect unless the patient has been experiencing a series of unpleasant dreams. In this case, the dosage may be split to a.m. and h.s. portions.

Tactical Issue: Poor Patient Response After Three Weeks

If the patient has failed to show any signs of response to 150 to 200 mg. of imipramine in three weeks' time, what are the chances of his responding to another tricyclic? Early and low-dose response to a tricyclic augurs well for the efficacy of that drug overall. Some improvement in sleep and energy level in as little as a week can occur in good responders. Conversely, if response to a tricyclic does not begin within 10 days to a dosage of 150 mgs. of imipramine, the chance that continuing that drug on higher levels for a longer period of time will produce acceptable antidepressant therapy is slight. For the non-responder, increased doses in the range of 250 mg. and over may induce no response at all; moreover, the increased dose may produce sedation or irritability and sleeplessness, dry mouth, urinary retention, constipation, and sweats without relieving depression. Sometimes at high doses (usually in excess of 300 mg.), the drug behaves like a neuroleptic rather than an antidepressant, as evidenced by the induction of movement disorders, including bradykinesia, rigidity, and tremor. When absent or unwanted effects appear, it is wise to taper the drug by 50 mg. every two days to avoid cholinergic backlash. The symptoms of this are nausea, abdominal cramping, diarrhea, and headaches. Delirium and convulsions are also possible side effects of sudden withdrawal.

Failure with the initial tricyclic reduces somewhat the chance of success with a second, although there are sufficient good results with a second choice tricyclic to warrant its use. The institution of the second tricyclic may be done in one of two ways. First, it may be given after the patient has been reasonably "drained" of the initial tricyclic. The second, and preferable, way is to phase in the second agent by substituting it gradually on a potency-equivalent basis or by making direct substitution on the same basis. For instance, desipramine may be given as a gradual or direct substitute for amitriptyline or imipramine. Desipramine in equivalent doses has a

more purely catacholaminergic effect than the aforementioned agents. Initial sedation is less, and the unpleasant anticholinergic effects are less in evidence.

Protriptyline is possibly an underused agent in retarded depression. It can serve well as drug of second choice. Dose response varies widely. Some patients find the drug stimulating; and it should be started in low doses, such as 10 to 15 mg. daily, which may suffice, or good antidepressant response may begin only at 60 mg. daily. We find that amitriptyline responders usually do as well on imipramine and that imipramine is a superior drug to amitriptyline because of its lessened anticholinergic effects. Sometimes amitriptyline is chosen first because of its supposed sedating effect. However, the sedating effect may linger and be more troublesome to the patient than helpful. In addition, dry mouth, constipation, and sweats are more troublesome with this drug than with imipramine or desipramine.

It is probably true that in some patients the side effects are an indication of the antidepressant effect of the agent. Most patients on therapeutic doses of any tricyclic will have some dry mouth and some mild constipation. Dry mouth is the most persistent and commonly encountered side effect. Amitriptyline is eight times more anticholinergic than desipramine and four times more anticholinergic than most other tricyclics, including imipramine. Alpha-blocking effects are more strongly induced by amitriptyline than by other tricyclics. Doxepin may be a drug of choice for some patients because it has very minimal if any alpha-blocking effect.

As we treat an increasingly aged population for depression, the tricyclics' effect on the heart becomes an important issue.[11] The administration of tricyclics to patients with conduction defects or with failure is best done by that psychiatrist who is skilled in treating that group of patients. Older patients or those with severe diabetes mellitus or other metabolic defects pose another problem. In general, in this group the side effects are enhanced. This group of patients is prone to develop orthostatic hypotension even on moderate amounts of the agents. Thus they should be started on low doses of tricyclics with the least anticholinergic effects. For instance, a severe diabetic in mid or late life is best begun on 25 mg. of imipramine (or possibly better yet desipramine); and over a period of weeks, the dose should gradually be raised to 75 mg. of the agent. Often, these patients cannot tolerate more than 50 to 75 mg. of the agents mentioned and do get relief from these low doses.

Given that the depressed patient has responded to a tricyclic such as imipramine 150 mg. daily to the extent that appetite, weight, sleep, and energy-level productivity have returned to normal and that the patient can face life with a certain optimism rather than hopelessness, self-sufficiency rather than dependency, self-esteem rather than worthlessness, modulated pleasure rather than nihilism, and given that the side effects consist of no more than slight dry mouth and minimal tendency to constipation, that his overall endocrinological and cardiac status remains good, how long should the patient be continued on the medication? There are no easy answers to this question which is at present under scrutiny. Tricyclic-responsive depressions may be either episodic, or they may represent a chronic condition with exacerbations of intermittent severer depression, forming a subgroup of primary affective illness. If a careful history has revealed reduplicable patterns in the past (e.g., the depressions are mostly in the fall and last typically for two or three months), then following the previous cycles, one may reduce the dosage by 50 mg. a week and discontinue the medication altogether if no recurrence of depression is encountered. The information concerning his previous cycles should be noted on the patient's chart so that one will be ready to begin the antidepressant again once the episode begins. All this is much easier to do in theory than in practice, since episodes are never really predictable. The pattern of recurrence may change. Sometimes mania or hypomania will appear in a patient who all his life has known only depression. On the other hand, the patient who has chronically subnormal mood and who does respond to tricyclic therapy should probably be maintained on the drug indefinitely, his depression "tested" by lowering the dose on occasion until the "tip" of the depression appears and then raising it slightly again. It is important to keep the tricyclic at the lowest level commensurate with patient benefit.

The tricyclics are drugs with low therapeutic index. Many have pointed out the in-built irony that the population treated by these agents is the most prone to make impulsive or well-thought-out suicide attempts. Since at each visit the patient is sent forth from the physician's office with a toxic amount of medication, care in prescribing an appropriate number of units must be taken. And what constitutes an appropriate number of units is in reality difficult to define. Only by knowing the patient well and having a firm therapeutic alliance with him can one begin to interpret his proneness for suicide. Establishing productive patient alliance and avoiding ambivalent dependency on the part of the patient is walking a fine line at times. Seeing the well-regulated patient at least once a month is desirable; and during the visit, simply handing the patient a refill without establishing more than cursory interpersonal contact with him is unwise. Yet both the physician's time and the patient's time and money are often very limited. One is thus forced to steer a difficult course. This is especially true for psychiatrists who deal with large outpatient populations. It is easy to lay down the rule that no patient should be sent out with more than an unrefillable week's supply of tricyclics. It is much better, if not, in a practical sense, impossible, to adhere to this rule.

What gram weight of a tricyclic is necessary to kill a patient who overdoses? Doses of over 2 grams can kill if the patient is left unattended.[12] The tricyclics

are drugs sharing the antimuscarinic effects of scopolomine and atropine. In the severe "anticholinergic syndrome," the patient has hot, dry, flished skin. The pupils are wide, leaving a narrow margin of iris; and they are sluggish in their reaction to light. The reflexes are increased. The mouth is bone dry. Urinary retention is developing or present. Bowel sounds are minimal or absent, and paralytic ileus is a danger. Delirium or coma may be present; tachycardia may lead to arrhythmia, a poor prognostic sign. The patient in overdose may be found slumped in a chair or stuporously in bed. The tongue may protrude, blocking adequate respiration and thus causing cyanosis. Directly, the patient is brought on an emergency basis to the hospital, where he is attended on the intensive care unit. Propanolol in doses of 1 to 5 mgs. i.v. is given for the arrhythmia.[13] Physostigmine is given i.v. up to 4 mg. and repeated at intervals.[14]

B. Monoamine Oxidase Inhibitors

After several months of failing to relieve the patient's depression by tricyclics, one either reconsiders the diagnosis or has the option of using a monoamine oxidase inhibitor (MAOI). Used in the decade that saw the development of the tricyclics, they were largely abandoned for ten or more years, since studies suggested that all but tranylcypromine were significantly less effective than the tricyclics.[15] In addition, the coup de grace was given to these drugs because of their reported dangerous side effects when combined with foods rich in tyramine. Tyramine is a pressor amine present in a large number of foods and beverages ranging from Chianti through pickled herring to figs and yogurt. When an MAOI is added to tyramine-rich foods, adrenergic outflow is set in motion, resulting in rise of blood pressure with consequent severe headaches, to possible hypertensive crisis, encephalopathy, and death. Some psychiatrists believe that these ill effects have been exaggerated, that they were sometimes unpredictably episodic in nature, and that they occurred when the tyramine content of ingested food and drink exceeded 12 mg. daily. Considered especially dangerous was the combination of MAOI's and tricyclics. The latter belief is, in certain circumstances, disputed today.

Do the MAOI's then have any place in modern antidepressant therapy? The answer is a qualified yes. First, as compared to the anticholinergic atropine and scopolomine effects of the tricyclics in therapeutic dosage, the MAOI's have very little, if any, such noticeable effect. Secondly, there is a subgroup of endogenous depressions that appear to respond well to this group of drugs after repeated tricyclic failure. This subgroup may consist of individuals who evidence strong anxiety and tension in their depressions. It may also contain those individuals who tend to run long periods approaching chronicity of marked dysphoria and anergia. The MAOI's can paradoxically sedate the anxious and energize the retarded anergic dysphoric.

One of the authors has treated a man in his early thirties who for a dozen years had more or less continuous psychiatric therapy. This included psychoanalytically oriented psychotherapy for several years, the use of lithium in effective doses, and finally efforts on various tricyclics, including imipramine and amitriptyline in very high doses, up to 400 mgs. a day. The tricyclics did not resolve the depression, and there were no anticholinergic effects or neurotoxic effects. After "draining" the patient from the imipramine he was taking, leaving a two-week gap of no medication, phenylzine was started in doses of 45 mgs. per day. There was no response in a week's time. When, however, the dose reached 90 mgs. daily, the patient responded dramatically over three days. Energy and sexual drive returned. There was no subjective dysphoria. No anticholinergic effects were present. The patient was, however, somewhat stimulated. Work tolerance increased markedly. The patient remained at a high pitch of performance without exhaustion. There was less need for sleep, the patient stating that at some level he realized tiredness at night but was not disturbed by it. His sleep became irregular, but his weight remained constant. During this period, he went through several major life adjustments without depression. Though lacking irritability on a psychic level, he tended to have an increased reserve of muscular strength and began a heavy program of exercise. Recently liver function tests (these being especially important) were normal. He is now stabilized on between 75 mg. and 90 mg. daily. He manages, without discomfort, to keep a diet free of excess tyramine and has had no hypertension.

The above patient responded well because of intelligence and a sense of responsibility. This is a key to the administration of MAOI's. There are many potential responders to whom the administration of these agents would pose grave dangers. In this group belong the very nervous and suggestible individuals with a low level of responsibility.

There are two MAOI's in use today. These are tranylcypromine (Parnate®) and phenylzine (Nardil®). Iproniazid (Marsilid) has been abandoned largely because of its capacity to induce severe liver toxicity. Tranylcypromine has a reputation for being somewhat more stimulant in its properties than phenylzine and for this reason is an MAOI of first choice for many clinicians. It also has a reputation of interacting somewhat more violently with tyramine. In our own experience, both tranylcypromine and phenylzine can cause either relaxation with some orthostatic hypotension or have an amphetamine-like stimulatory effect. This brings our attention to the interesting structural similarity among amphetamine, methylphenydate, and both the hydrazine and non-hydrazine MAOI's. Yet the MAOI's are not addictive and to our knowledge do not in therapeutic dosage produce the dangerous, paranoid toxic psychoses the amphetamines do.

The MAOI's are of interest historically, insofar as

they grew out of a search for anti-tuberculosis drugs. It was found that when isoniazide was administered to tubercular patients, mood elevation, indeed physical activation, took place. One of the authors recalls a friend who in his early twenties was afflicted with clinical tuberculosis. For years after clinical illness, he took isoniazide. During that time he was a physically active and ebullient individual. His isoniazide was withdrawn, and shortly thereafter he lapsed into severest depression and ended his life in self-immolation. No one had considered the fact that in withdrawing him from an anti-tubercular drug they were removing a potent antidepressant from him.

Readers may have heard of the present-day research concerning the enhanced antidepressant efficacy of combining tricyclics with monoamine oxidase inhibitors. Research does indicate that the combination can be given safely.[16] However, evidence that this is a superior way to treat refractory depression is not fully accepted. This work is experimental, and therefore the authors believe it to be not yet applicable for standard medical practice.

Candidates for MAOI's need careful psychiatric evaluation and especially close follow-up. Should a family physician decide to use MAOI's, a consultation with a psychiatrist is desirable. Patients who are receiving MAOI's should carry such identification on their persons. Should the patient suffer a sudden increase in blood pressure or a sudden headache in the course of treatment, he should be instructed to go to the emergency room of his hospital. Treatment consists of the alpha-blocker, phentolamine, Icc. parenterally.

C. Lithium Carbonate in Depression

We have briefly discussed the role of lithium in mania. Does this drug have a place in the management of depression? Opinion is varied. One school suggests that lithium carbonate at relatively high maintenance mEq levels is an effective antidepressant and may have a special place in preventing the recurrence of depression. The authors believe that the ion within "therapeutic" lithium levels is associated with clinical improvement. This may obtain in the case of those "depressives" who undergo the motor and behavioral signs of mania with the painful dysphoria characteristic of endogenous depression. That such "mixed" episodes occur has been increasingly brought to our attention. However, this concept is not new, having been recognized by Emil Kraepelin.[17] Both of us have treated depressives apparently refractory to tricyclics who achieved greater mood stability and significant lessening of depression when regulated on lithium levels less than 1 mEq and who did not have to undergo significant lithium toxic side effects to achieve this improvement.

Lithium treatment implies long-term treatment, and the patient may require months of therapy to get maximal results. The dysphoric lithium responder may represent a subform of primary affective illness, possibly including patients given to more brittle rapid cycling and anxiety and those given to painful obsessive ruminations. The latter, especially, are notoriously difficult to treat with tricyclics, and they respond only indifferently to neuroleptics. Possibly it is wise to use electroconvulsive therapy as the method of first choice for these refractory patients.

III. Neuroleptics

Neuroleptics constitute another group of drugs used in the treatment of severe depression. The neuroleptics have as their cardinal pharmacokinetic effect the antagonism of dopamine in the brain, and probably through this mechanism induce behavioral quietness.[18] The group includes the phenothiazines: chlorpromazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, and a number of others; the butyrophenones, of which haloperidol is the representative and one of the most popular and flexibly used antipsychotics today; the thioxanthenes: thiothixene, chlorprothixene, and certain new compounds such as the indol derivative molindone and the new dibenzazepine loxapin. All these drugs share essentially the same effectiveness in treatment-amenable illnesses. Milligram potency varies widely. Idiosyncratic response, which is unpredictable, is also a factor. All these drugs have anticholinergic effects and alpha-blocking effects stronger probably in the low potency drugs. All of them—probably because of their CNS antidopamine activity—can and do cause movement disorders ranging from akinesia to long-term florid choreo-athetoid disturbance. These drugs are less specific for depression than the aforementioned and are undoubtedly used to cover far too many areas of mental illness.

Do these drugs which are nonspecific for endogenous depression have any place in its treatment? Under special but limited circumstances they do have a place, although they are more often overused than neglected. Traditionally, the so-called "agitated depression" as typified by involutional melancholia (a diagnostic category which is less than satisfactory) have been viewed as more neuroleptic responsive than tricyclic responsive. Some patients often designated as involutional agitated melancholics are better described as manic-depressive patients in a mixed state of mania and depression. Thus possibly many neuroleptic responsive melancholics should be afforded the opportunity of lithium therapy, using the neuroleptics to accomplish, in their nonspecific way, the relief of the agitation and anxiety which are component parts of "agitated" or "mixed" states.

It is very important to remember that the "side effects" of the neuroleptics can cause symptoms which are difficult to distinguish from symptomatology of depression and thereby lay the basis for iatrogenic illness to be confused with the disease to be treated. Anergia, abulia, affective dampening, uncommunicativeness, restless movements, and motor and psychic slowing are all symptoms of depression; and all can be caused as well by neoroleptics. This danger is minimized by the physician's having a high index of suspicion for neoroleptic intoxication. As well, he should use doses that keep him within the non-toxic

boundaries. The essential need consists of encouraging the "specific" agents—tricyclics and lithium—to do their task and to eliminate the neuroleptics as soon as possible. If the patient is unresponsive to specific antidepressant chemotherapy, a course of electroconvulsive treatment should be completed. This course can then be followed by an attempt to stabilize on lithium carbonate or a tricyclic in the hope of preventing recurrence.

Once again, the ideal situation and the realities of treatment need do not always coincide. One of the authors has treated three patients with cardinal signs of endogenous depression and with the depressions tending towards chronicity but with severe exacerbations lasting at least several months, with no manic episodes to break the pattern. These patients were afflicted with suicidal impulses. Possibly they belonged in the schizo-affective group, with affective symptoms strongly overriding the schizoid ones. The patients responded to neither antidepressants nor phenothiazines individually. They did, however, respond well, and have done so in each case for more than two years, on a regimen of tricyclic and neuroleptic. Two of the patients have done well on desipramine 150 mg. daily and thioridazine 300 mg. daily. The third responded rather dramatically on low doses of oral fluphenazine (ca. 3 mg. daily) and 100 mg. of imipramine daily. The combination of neuroleptic and tricyclic was not undertaken lightly but has proved useful in some atypical primary depressions.

When adding a neuroleptic in the treatment of depressed patients, we are guided by the following principles and caveats:

1. The capacity of neuroleptics to cause movement disorder: Thioridazine is a useful drug in this regard, for on an effective-dose basis its capacity to induce movement disorder is possibly the lowest among the marketed neuroleptics. On the other hand, it has stronger anticholinergic effects than most, a feature which is not desirable when using other anticholinergic medication.
2. Possibly the piperizines, especially fluphenazine, have the least sedating and anticholinergic properties on a dose-equivalent basis. They are, however, the most likely to induce movement disorder. Thus in trade-off, if we are especially desirous of avoiding sedation, we employ oral fluphenazine cautiously in low doses (under 15 mg. daily).
3. Haloperidol is so popular today that some may attribute to it beneficial properties not shared by the other antipsychotic agents. However, in our clinical setting we have found it to be used, especially while waiting for lithium adjustment, in doses too high for the need (i.e., in excess of 30 or 40 mg. a day), doses which have produced marked mental dulling, bradykinesia, rigidity, and tremor in mood-disordered patients. Therefore, it is usually preferable to start with a piperidine such as thioridazine as indicated above or possibly mesoridazine when adjuncts are needed to more specific treatment.

We take into consideration the fact that neuroleptics are, like the tricyclics, anticholinergic drugs and that their addition compounds the anticholinergic problem associated with the tricyclics. There is some evidence also that the combination of these drugs does indeed enhance the potential for cardiotoxicity.

Benzodiazepines and the Treatment of Depression

Benzodiazepines constitute a fifth group of drugs used, generally unwisely, in depression. Almost every patient we have interviewed who gives us a history of recurrent mood disorder has been treated with one or more benzodiazepines. The benzodiazepines continue to be a problem for medicine in general and for psychiatry in particular. Diazepam, flurazepam, chlordiazepoxide, oxazepam, and more recently lorazepam constitute collectively today as much a cultural phenomenon as a therapeutic modality. Overused, they are apparently prescribed almost indiscriminately to alleviate the existential burden that belongs to normal living. Any psychiatrist who has worked in an outpatient setting knows all too well how patients batter at his office door and will power as well to obtain these agents. The benzodiazepines are somehow frequently obtained by people who are not ill but who for one reason or another are unhappy and nervous.

The benzodiazepines are indicated for certain clinical emergencies as well as in the short-term treatment of acute situationally caused anxiety states. Their use in diagnosed mood disorder is not warranted. Recently some evidence has been presented that chlordiazepoxide given in combined dosage with amitriptyline may enhance the effectiveness of the amitriptyline.[19]

Are Fixed Combination Preparations Useful?

A final issue in the usefulness of fixed combination preparations in the management of depression. These combinations are much advertised and in common use. Most popular is a tablet which contains a mixture of perphenazine and amitriptyline. These preparations are best avoided. They constitute a kind of "shotgunning" against a cluster of possibly poorly defined symptoms.

If both a neuroleptic and antidepressant are called for, it is desirable for the clinician to reserve unto himself the option as to which drugs and how much of each he should use.

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Arterial Sigmoid Fistula

Treatment by Fistula Exclusion Without Graft Excision

IRVING L. KRON, M.D. AND RICHARD C. DILLIHUNT, M.D.*

BRIEF SYNOPSIS

An unusual case of arterial to sigmoid fistula following aortic surgery is presented. This complication was treated successfully by fistula exclusion without graft excision. The technique and theoretic implications are described.

Arterial-enteric fistula is a dread complication of aortic surgery. The mortality rate in the literature has been as high as 80%.[1,2] Though usually a late postoperative complication, it may occur as a primary complication of aneurysms.[3]

The most common arterial to enteric fistulae have been aortoduodenal, usually following surgery for abdominal aortic aneurysm. Fistulae involving sigmoid colon are much more unusual and have been reported rarely.[4]

We recently have encountered a patient with lower gastrointestinal bleeding due to a fistula between the iliac graft and sigmoid colon. Our successful result based on bypassing the involved area and exclusion of the fistula forms the basis of this report.

CASE REPORT

An 83-year-old white male had a 12 cm. abdominal aneurysm resected in August 1975. A bifurcated Dacron graft was placed between the aorta and iliac artery. The left iliac artery was also aneurysmal and therefore was bypassed and oversewn. His immediate postoperative course was complicated by systemic Candida sepsis and later bacterial sepsis. After an appropriate course of antibacterial and antifungal therapy, he was discharged four weeks after aneurysm resection.

The patient was readmitted in March 1977 for suprapubic prostatectomy. At the time of surgery, he was noted to have a left lower quadrant nonpulsatile mass. This was felt to represent the oversewn iliac aneurysm.

In July 1977, the patient developed brisk transient bright red rectal bleeding which ceased spontaneously. A few days later this recurred, and he was readmitted. He was noted to be pale and cachectic but normotensive. His significant physical findings were a left lower quadrant pulsatile mass and bright red blood clots per rectum. A retrograde femoral angiogram revealed a false aneurysm at the left iliac anastomosis. The enteric fistula was not identified since the patient was not actively bleeding (Fig. 1).



Fig. 1

The evening of admission the patient suffered an exsanguinating rectal hemorrhage. He was resuscitated and taken to the operating room.

Transabdominal exploration revealed a 10 by 15 cm. pulsatile left lower quadrant mass noted to be bound to sigmoid colon (Fig. 2). The mass had an inflammatory appearance with firm adhesions to surrounding structures. A segment of the proximal left iliac limb of the Dacron graft proximal to the fistula was excised and oversewn. A sigmoid loop colostomy was created but not opened intraoperatively. Both common femoral arteries were exposed through separate incisions and the left external iliac artery was ligated to prevent backflow into the fistula. A femoral bypass was constructed using saphenous vein to provide blood flow to the left leg. It was elected not to remove the inflammatory mass and the underlying graft material because of the patient's precarious condition, the amount of difficult dissection that was envisioned and the chance of gross fecal contamination (Fig. 3).

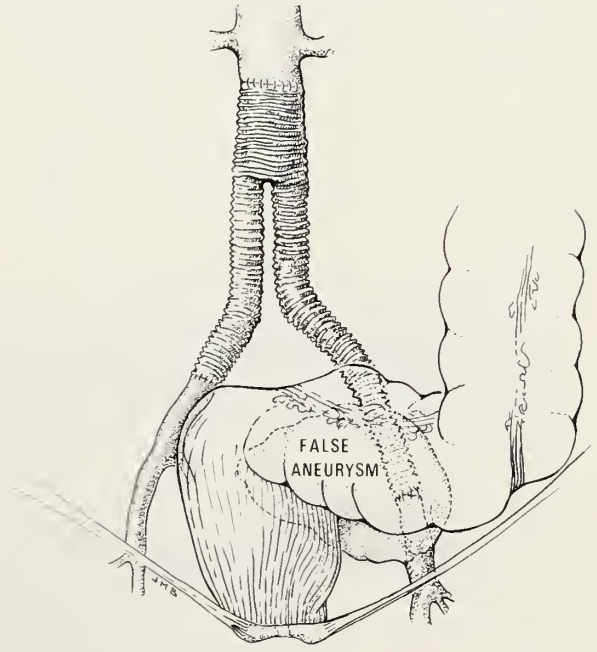


Fig. 2

The postoperative course was entirely benign. Excellent blood flow was present in the left leg and no further rectal bleeding ensued. The sigmoid loop colostomy was opened on the second

*From the Maine Medical Center, Portland, Maine 04102.

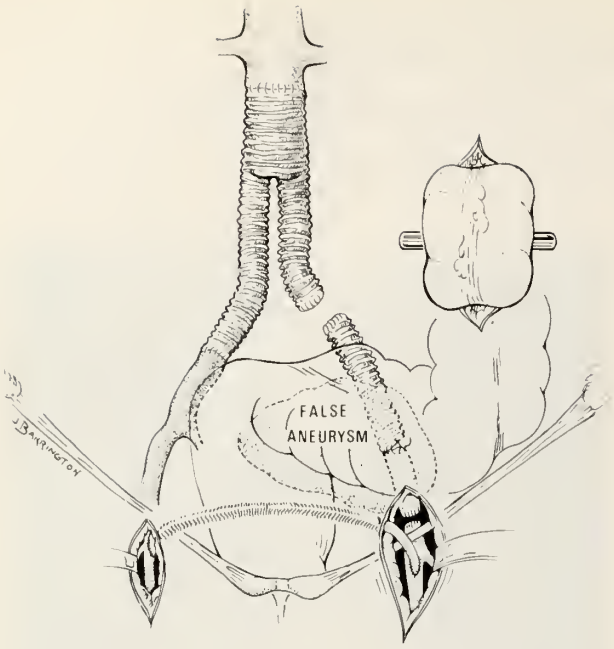


Fig. 3

postoperative day. The patient was discharged on the 14th day. The excised portion of the proximal graft showed no bacterial growth. The patient is alive and symptom-free sixteen months postoperatively.

Discussion

Several mechanisms have been described for the development of arterial-enteric fistulae. The Dacron prosthesis has been postulated to set up a foreign body reaction to adjacent bowel and eventually erode into it.[5] Low-grade infections in the suture line may cause fistula formation either directly or by causing a false aneurysm which secondarily erodes into bowel.[1,6] As seen in our patient, false aneurysm may be present months prior to fistula formation.[7] Primary bowel pathology as in prior intraoperative injury to duodenum may be a contributory factor.[8]

The basic problem with this entity has been the question of whether an aortoenteric fistula always connotes graft sepsis. Several successful case reports describe various forms of primary repair or regrafting if overt intraoperative sepsis is not present.[8,9,10]

Others state that all aortoenteric fistulae should be considered infected either primarily or second to contamination from intraluminal bowel contents.[2] Assuming the graft is septic, the consensus for treatment seems to be extra-anatomic vascular bypass followed by graft excision.[2,7,11,12]

Ehrenfeld compared mortalities of various treatments of arterial enteric fistulae depending upon the method utilized.[2] Eighty-seven percent mortality was present in those treated by local repair as compared to thirteen percent in which excision and extra-anatomic grafting was carried out. It is evident that prosthetic grafts should be considered infected in most cases of aortoenteric fistula.

Continued on Page 397

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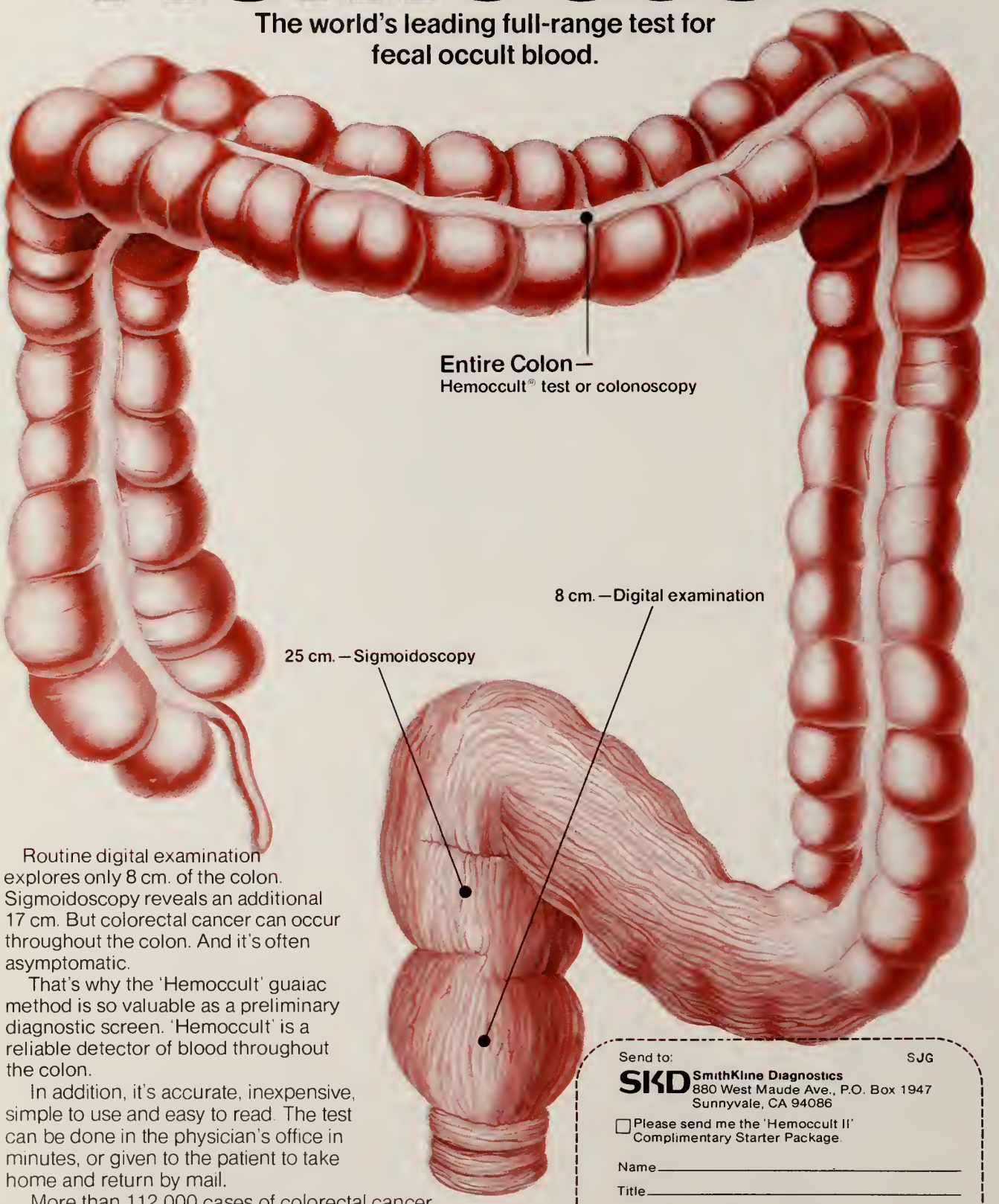
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Sepsis tends to stay fairly localized in an unthrombosed graft.[13] Therefore, in distal suture line involvement, such as seen in localized groin sepsis, adequate treatment would consist of some form of extra-anatomic bypass and excision of the involved limb of the graft. This can be done as a staged procedure with primary defunctionalization of the involved graft limb and removal of the graft at a later date.[14]

Our patient was treated by defunctionalizing the fistula between the distal left iliac graft suture line and sigmoid colon. This was done by proximal colostomy to avoid further bowel contamination and simultaneous isolation of the involved graft segment. Femoral femoral bypass with autogenous saphenous vein was used to bypass the isolated iliac graft. If graft excision has been performed, this would have been in concordance with the previously mentioned treatment of septic grafts. However, graft excision in our patient would have involved extensive dissection through an inflammatory mass with gross fecal contamination. It was elected, therefore to defunctionalize the involved graft and treat it with preoperative and postoperative antibiotics.

There is both experimental and clinical evidence that grafts can be left in infected beds if aggressively treated with local and parenteral antibiotics.[15,16]

Our patient, fourteen months postoperatively, has no evidence of continued infection.

Summary

Arterial-enteric fistula involving sigmoid colon is an unusual entity. Since the distal iliac graft suture line communicated with the open colon lumen, localized graft infection must be assumed. Ideally, this should be treated by vascular bypass and excision of the involved graft limb. We have presented a case in which defunctionalization of the graft fistula and bypass without graft excision was successfully performed. This alternative procedure merits consideration in a critically ill patient.

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Posterior Fossa Arachnoid Cysts

William H. Leschey, Jr., M.D.*

Arachnoid cysts occur in supratentorial, infratentorial or spinal locations, but there is a predilection for the posterior fossa. The clinical manifestations of increased intracranial pressure from obstructive hydrocephalus have been the main presenting symptoms and signs of previously reported cases of posterior fossa arachnoid cysts.[6,8,11] Computed tomography (CT Scanning) now permits diagnosis in an earlier pre-hydrocephalic stage.

Case Reports

Case 1. M.W. is a seventeen-year-old woman admitted to MMC on 1-2-79 for evaluation of disabling dizziness and an abnormal CT Scan. Six months prior to admission, she developed rotational vertigo associated with autonomic symptoms. The vertigo was recurrent over the next few months and the patient was not attending school. Caloric tests and electronystagmography were reported as abnormal. Her most recent complaints were dizziness, trouble with balance and mild generalized headaches.

Prior to admission, outpatient evoked potential studies (visual, brain stem auditory and somatosensory) were normal, but the CT Scan showed a midline posterior fossa cyst above the cerebellum and just below the tentorium (Figures 1 and 2).

The neurological and ENT examinations were entirely normal. The patient had no hearing loss, papilledema, positional or spontaneous nystagmus, ataxia or other cerebellar signs. The delayed static images of the radionuclide brain scan were positive. An area of increased activity was present in the midline of the posterior fossa (Figure 3).

Bilateral vertebral angiograms revealed no tumor stain or vascular displacements. A pneumoencephalogram showed no shift of the fourth ventricle and normal posterior fossa cisterns. CSF was normal including immunoglobulin percentage.

The patient was treated non-operatively because of the high risk of surgery relative to the severity of her symptoms. She has returned to school.

Case 2. M.L. is a twenty-six-year old man admitted to MMC on 1-15-79 because of intermittent pain, numbness and weakness of the left upper extremity since childhood. At age seventeen years, he had a negative cervical myelogram. His recent complaints consisted of unsteadiness in walking, stiffness of the legs and left arm weakness. On exam, rotary clockwise jerk nystagmus was present on gaze to the left. Fundi were normal. The left biceps and triceps deep tendon reflexes were absent and the left radial reflex was inverted. Loss of pain and temperature sensation was present over the left shoulder and arm. Position sense was also impaired in the left hand. In addition to weakness in the left arm and a left Hoffman Sign, there was a mild spastic paraparesis with absent superficial reflexes and equivocal extensor plantar responses.

CT Scan revealed a right extra-axial cerebellar cyst with displacement of the fourth ventricle from right to left (Figure 4). Pantopaque® posterior fossa myelogram showed mild cerebellar tonsillar herniation and no radiographic evidence of syrinx. The preoperative diagnosis was right cerebellar extra-axial cyst with a probable associated syringomyelia. A right suboccipital craniectomy was performed. The major portion of the cyst was removed and the remaining membrane was marsupialized. The pathology report confirmed the arachnoidal nature of the membrane. Following surgery, the nystagmus and unsteadiness disappeared, but the other deficits have persisted to date.

Discussion

Arachnoid cysts are classified as primary or secondary.[8] Primary cysts are considered congenital or developmental anomalies. Secondary or acquired cysts are hypothesized as resulting from infection or trauma.

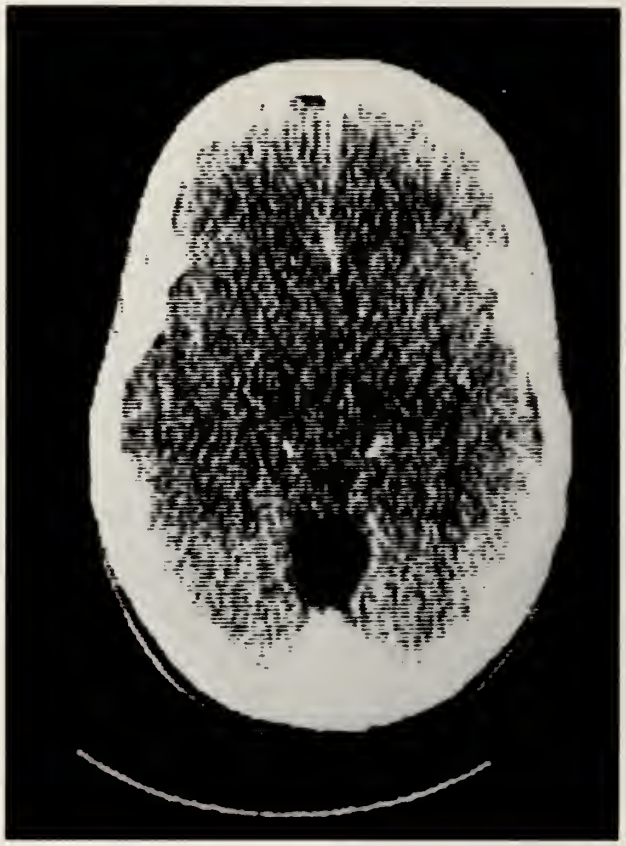


Fig. 1. Case one CT Scan: Midline posterior fossa cyst.

The pathological evidence for cysts being primary or congenital includes the finding of tufts of ectopic choroid plexus, as well as regular ependymal cells, in the cyst walls.[11] These embryonic rests are thought to develop secretory functions and lead to cyst formation. The midline location of cysts which is the most common site also seems to favor an embryonic or developmental process.

The role of trauma as a predisposing cause of infratentorial cysts is uncertain. The importance of minor, or even severe head trauma, in causation of a cyst discovered sometime later is difficult to assess. The argument for infection as an etiological factor seems more valid since localized infection can be correlated with development of a cyst in the same region. For example, a cerebello-pontine angle cyst may complicate a severe mastoiditis. Multilocular cysts are well known to develop in the presence of adhesive arachnoiditis; however, when walls of large unilocular posterior fossa cysts have been examined pathologically in cases suspected of being secondary

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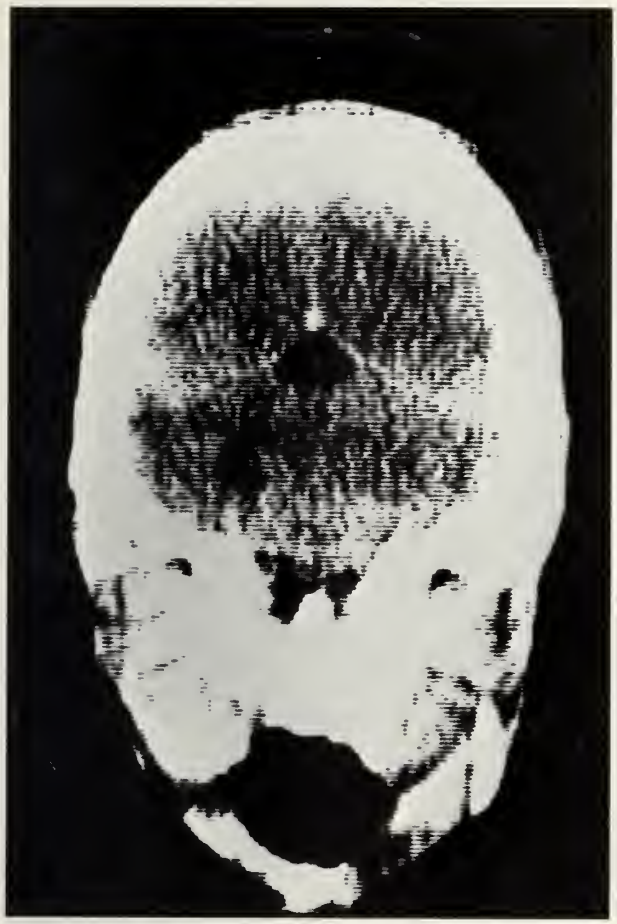


Fig. 2. Case One CT Scan: Coronal view showing low absorption cyst just beneath the tentorium.

to infection, inflammatory cells have been absent.[6]

The frequent association of other congenital anomalies with posterior fossa arachnoid cysts provides additional evidence for a developmental disorder. Increased incidence of craniovertebral anomalies including platybasia and basilar impression, syringomyelia, agenesis of the corpus callosum and Arnold-Chiari malformation have been reported in association with posterior fossa cysts.[2] Elaborate theories have been proposed to explain these associations. According to one such theory, any of the anomalies are secondary to failure of the fourth ventricular foramena to develop normally in the rhombencephalic roof.[2]

The Dandy-Walker syndrome has been traditionally considered the developmental anomally to occur when there is atresia of the foramena of Luschka and Magendie. In this situation, a balloon-like dilitation of the fourth ventricle occurs in association with agenesis of the cerebellum. According to the theory of a common etiological process for all infratentorial cysts, the Dandy-Walker anomaly occurs when the rhombencephalic roof remains intact; but when the roof splits into two layers, an arachnoid cyst will form. The extra-axial cyst may remain as a diverticulum of the fourth ventricle or later become detached. This theory among others of cyst genesis is disputed.

Within the posterior fossa, the most common location of arachnoid cysts is in the midline and posterior to the cerebellum.[6,8] Of the midline cysts that are posterior to the cerebellum, the majority are inferior rather than superior. Tentorial notch and clivus are less common midline locations. Off the midline, the cerebellar hemisphere and the cerebellopontine angle are the most common sites. Multiple arachnoid cysts in different locations may occur in a single patient.[6]

By the time the diagnosis was discovered, most of the previously reported patients with posterior fossa cysts had developed increased intracranial pressure secondary to obstructive hydrocephalus.[6,8] Adults presented with headache, nausea, vomiting and papilledema. Infants and children presented with enlarging head size and other manifestations of hydrocephalus.[4] The average duration of symptoms prior to diagnosis varied from six months in one series to four years in another series.[6,8] One patient had symtoms for thirty-three years. The time from onset of symptoms to diagnosis reflects the difficulty in diagnosis in the early, pre-hydrocephalic stage which may be prolonged and last for years.

The clinical findings are usually nonspecific and suggest posterior fossa neoplasm. There is nothing in the clinical examination to permit differentiation of an arachnoid cyst from any other expanding posterior fossa lesion. An exception would be an infant with an enlarged head which transilluminates in a characteristic pattern. The posterior inferior aspect of the skull of children less than a year of age who have posterior fossa extra-axial cysts is described as transilluminating in a specific lobulated configuration distinct from the triangular shape seen in the Dandy-Walker syndrome.[4] No such clues are found on physical examination of older children and adults with cysts.

The clinical signs usually do not permit localization within the posterior fossa, but rarely precisely localizing findings are present. Cysts in the cerebellopontine angle present characteristic signs simulating an acoustic neurinoma.[6]

The episodic and positional nature of the symptoms, primarily headache and dizziness, in reported cases are described as characteristic of posterior fossa arachnoid cysts, and are postulated as correlating with intermittent obstructive hydrocephalus or with changes in cyst volume.[11] Cases have been reported in which the patients could relieve severe headache by changing head position.[9] Recurrent monobrachial weakness and numbness along with cranial nerve signs have been reported and are similar to the clinical features of case two.[5] In another reported case, remissions and exacerbations of nystagmus and unilateral arm weakness from a clivus arachnoid cyst closely simulated multiple sclerosis. The author suggests that complaints of headache or neck pain predating the other symptoms might permit differentiation from multiple sclerosis.

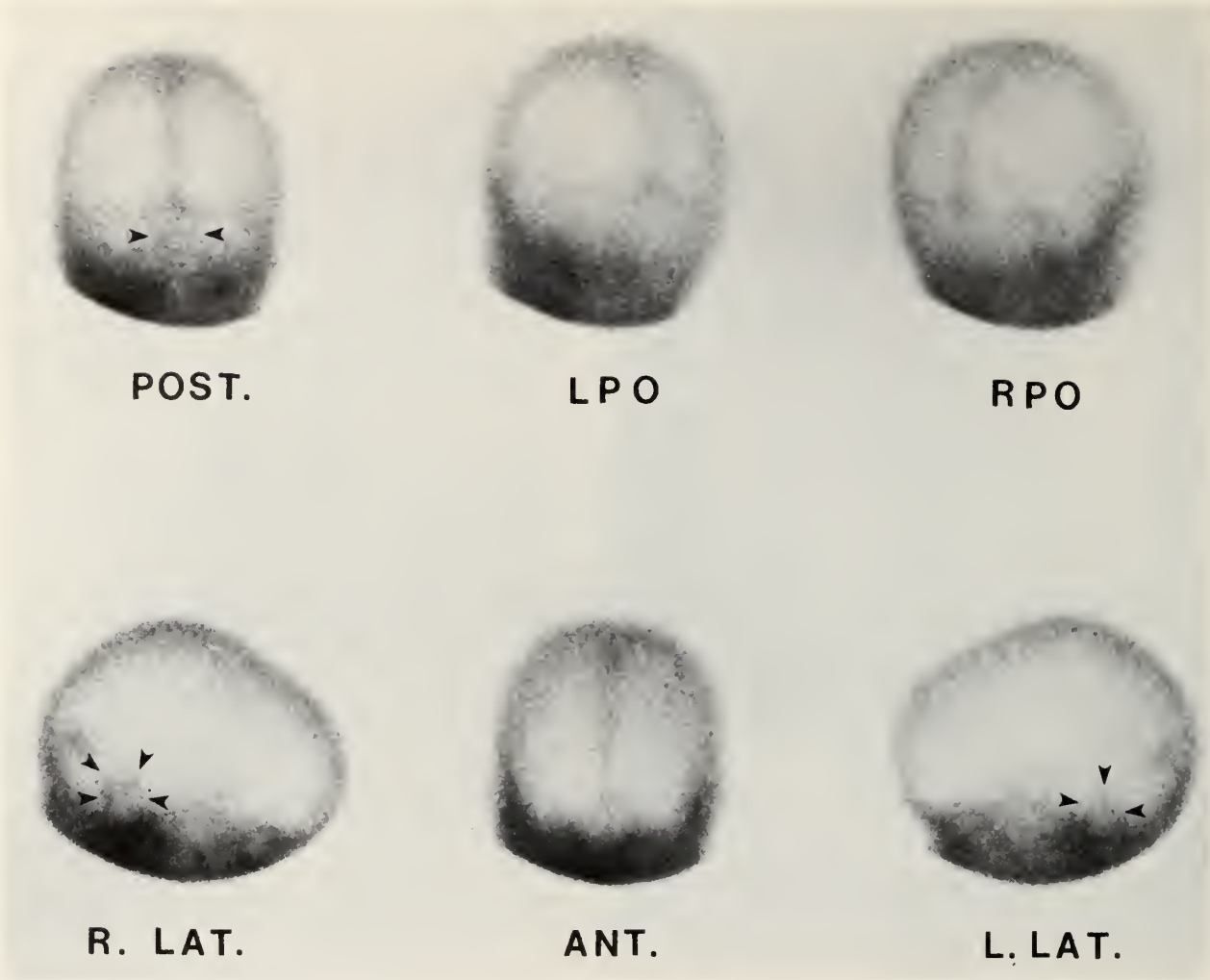


Fig. 3. Case One RN Scan: Arrows delineate area of isotope accumulation in the midline of the posterior fossa.

The diagnosis of posterior fossa cysts has traditionally depended on angiography or air studies, but now is more easily made by CT Scanning. Plain skull films provide only indirect clues. Non-specific x-ray evidence of increased intracranial pressure is often present. A large posterior fossa with high positioned torcula and lateral sinuses can occur with posterior fossa arachnoid cysts, but these x-ray changes are more characteristic of Dandy-Walker syndrome. An associated cranio-vertebral anomaly may be evident on the skull films.

The angiographic features of posterior fossa arachnoid cysts have been well described in the pre-CT scan era, and the differential diagnosis from Dandy-Walker cysts has been discussed in detail.[4,10,12] All cysts appear as avascular areas or clear spaces. In extra-axial arachnoid cysts, various displacements of normal appearing posterior circulation arteries and the cerebellar blush occur, consistent with the location of the cyst. In the Dandy-Walker syndrome, the cerebellar arteries are often absent or hypoplastic, and the cerebellar blush is absent or small.

Air contrast studies were employed widely in the evaluation of patients with posterior fossa arachnoid cysts prior to the availability of CT scanning. A ventriculogram was the procedure of choice in patients with papilledema and increased intracranial pressure, and a pneumoencephalogram was often performed in absence of pressure phenomena. The main limitation of air studies is the fact that air often times does not fill the cyst. When the cyst did not fill with ventriculography, the preoperative diagnosis prior to the CT scan era was usually a posterior fossa mass, and the cystic nature of the lesion went unappreciated until surgical exploration.

When employed, pneumoencephalography via the lumbar route is more likely to fill a posterior fossa cyst, and permit a correct diagnosis.[6,7] Even so, the ventricular system may not fill due to distorted anatomy, and preoperative information may be incomplete. Air study criteria to differentiate a capacious cisterna magna from a retro-cerebellar cyst have been detailed, and the angiographic features also help make this differential diagnosis.[8]

Isotopes have been employed in the evaluation of patients with posterior fossa cysts. Radionuclide

Continued on Page 401

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*Incidence 3% to 9%.

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Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

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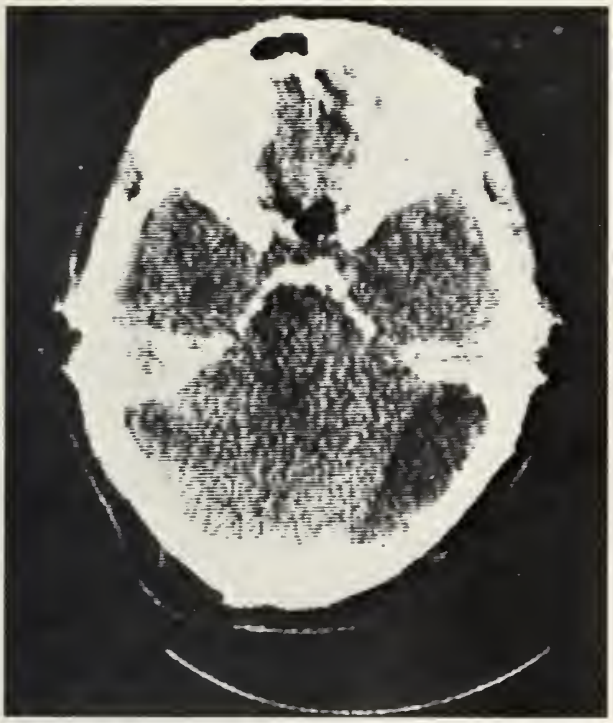


Fig. 4. Case Two CT Scan: Right posterior fossa cyst with right to left shift of fourth ventricle.

brain scans are reported as showing characteristic displacements of the torcula and transverse sinuses.[1] Similar patterns of a high positioned torcula and an acute angle where the transverse sinuses meet the torcula have been described for both the Dandy-Walker anomaly and posterior fossa arachnoid cysts.

Concentration of isotope in the cyst after intravenous injection has not been previously described, and would not be predicted on the basis of the usual pathology. The cysts being extra-axial, the blood brain barrier remains intact. Therefore, a localized pick-up on the static images of a radionuclide scan is unexpected. The cyst walls have been reported as sometimes having more vessels than present in normal arachnoid, and this possibly may account for concentration of isotope within the cyst. The possibility of Case One with a focal radionuclide scan representing some other type of cystic tumor (such as a dermoid or epidermoid) exists, of course, since the diagnosis is pathologically unverified.

Radionuclide ventriculography and cisternography have also been useful in selected cases, and sometimes can help differentiate a Dandy-Walker cyst from an arachnoid cyst.[1,3] An arachnoid cyst often fills when isotope is injected into the lumbar subarachnoid space, and the Dandy-Walker cyst usually fills only with ventricular injection of isotope. Exception to these filling patterns do occur, and the results must therefore be integrated with the other information. Prior to the CT era, injection of isotope directly into the cyst and study of the subsequent dilution were employed to calculate cyst size.[4]

The CT scan provides a non-invasive modality to differentiate infratentorial cystic lesions from solid tumors and has greatly simplified the diagnosis of posterior fossa cysts. Angiography may still be needed to differentiate a cystic tumor from an arachnoid cyst, or from a Dandy-Walker fourth ventricular cyst. In any event, CT scanning permits early diagnosis before the development of intracranial hypertension, as in the two reported cases in this paper. CT scanning also creates the opportunity for asymptomatic, coincidental posterior fossa cysts to be discovered in patients with neurological symptoms from other causes. This possibility should be considered in the formulation of a treatment plan in patients with minimal symptoms, as in Case One.

The definitive treatment of posterior fossa arachnoid cysts is suboccipital craniectomy and excision. In some cases, ventriculostomy drainage or a shunting procedure may be advisable prior to cyst removal.[6,8] In rare cases of a cyst in an inaccessible location or in a patient who is elderly or with other serious medical problems, a simple shunting procedure or cyst marsupialization may be the most appropriate approach. Surgery usually results in significant improvement, but operative mortality is significant: 10% in a series from Japan and 20% in a series from the Mayo Clinic.[6,8]

Failure to improve following surgery should lead to considerations of posterior fossa hematoma, postoperative obstructive hydrocephalus, re-accumulation of fluid within remaining remnants of the cyst wall or the possibility of an additional undetected cyst. Follow-up CT scans are indicated in the postoperative period, and a shunting procedure is sometimes needed at a later time.

Summary

Two cases of posterior fossa arachnoid cysts without increased intracranial pressure or hydrocephalus are presented.

In one case of a midline superior subtentorial cyst, the patient presented with minimal symptoms and a negative neurological exam. Contrast studies revealed absence of tumor stain, no mass effects or shift, and the patient was treated non-operatively. The radionuclide brain scan suggested isotope accumulation within the cyst.

In the case of a lateral cerebellar hemispheric extra-axial cyst, the patient had multiple neurological deficits, a negative radionuclide scan and a suspected associated syringomyelia. There was mass effect with significant shift of the fourth ventricle on CT scan, and the patient was treated operatively.

The pathological classification, common locations within the posterior fossa, usual presenting symptoms and signs, results of diagnostic tests and treatment of infratentorial arachnoid cysts are reviewed.

CT scanning provides early diagnosis in the pre-hydrocephalic stage. Since there is a significant operative mortality, treatment decisions may become more difficult, especially in the patient with minimal symptoms.

Continued on Page 405

Carcinoid Tumors at MMC — 1955-1978

Part I — Bronchial

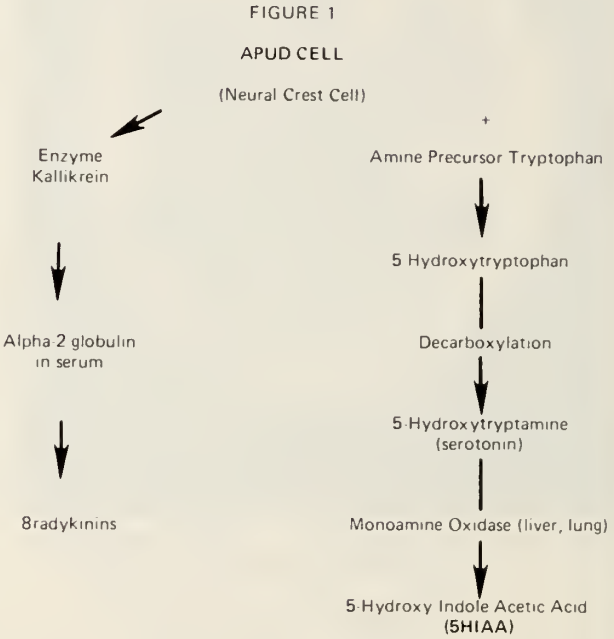
PETER K. CARTER, M.D.*

A review of the Maine Medical Center experience with carcinoid tumors over the period from 1955 to 1978 indicated several differences in incidence and clinical presentation from those reported in the literature. These differences are described in two reports, the first relating to bronchial carcinoids and the second to subdiaphragmatic tumors.

Because of the variable metabolic effects of certain carcinoid tumors, a brief historical perspective and summary of basic biochemistry is appropriate. In 1839, Merling[1] provided the first gross description of a tumor of the appendix now thought to be a carcinoid. With microscopic evaluation, Lubarsh[2] established the Crypts of Lieberkuhn as the origin and ten years later in 1888, Kultschitzky[2] identified granular cells in the crypts that still bear his name. In 1909, Obernorf[1] emphasized the "benign" nature of these tumors and introduced the term—"Karzinoide"—meaning resembling carcinoma. Also, at the turn of the century chromates were found to stain the granules yellowish brown and silver stain affinity resulted in metallic black;[2] thus, the familiar terms: "enterochromaffin" and "argentaffin" tumors.

The endocrinological and biochemical manifestations of the rare syndrome have fascinated investigators and resulted in intense study (Figure 1). In 1930, Vialli and Ersparnes[1] isolated from the gastrointestinal mucosa and extract—"enteramine"—that caused smooth muscle to contract. "Enteramine" was believed to be produced by the Kultschitzky cells; however, ten years later Rapport and Page[1] isolated from beef serum a substance they referred to as a "nuisance interferring with their experiments." The isolate was called "serotonin." Not until 1952[1] was serotonin found to be the same as enteramine—5-hydroxytryptamine, one of the major bioactive amines in the carcinoid syndrome. Pearse[3] in 1968 grouped all carcinoid tumors under the APUD cell theory (Amine Precursor Uptake Decarboxylation). Radioactive tagging[2] has traced the migration of neural crest cells during embryological development to the foregut, midgut, and hindgut locations. The cells retain an ability to take up amine precursors and decarboxylate them into bioactive amines (Fig. 1). The amine precursor for the Kultschitzky cell is the essential amino acid tryptophan. Unable to syntheside an indole ring, man must derive tryptophan from his diet. Normally one to two percent[4] of dietary tryptophan is utilized from serotonin synthesis and small quantities of serotonin

FIGURE 1



	ref
1930 – Enteramine	(1, 2)
1940 – Serotonin	(1, 2)
1952 – Serotonin-enteramine	(1, 2)
1968 – APUD cell	(1, 2)

are released from the granules and rapidly taken up by platelets. Any free serotonin is catabolized primarily in the liver but also in the lung to 5-Hydroxy Indole Acetic Acid (5HIAA) and excreted in the urine. Sixty percent of ingested tryptophan is usurped by a carcinoid tumor. The classic syndrome (diarrhea, flushing, endomyocardial fibrosis with right heart failure, asthmatic wheezing, pellegra-like syndrome, and arthopathy) will not manifest itself until there are massive liver metastases which drain into hepatic veins without serotonin degradation. Exceptions to this are bronchial,[13] testicular, and ovarian[2] carcinoids whose bioamines are secreted systemically and by-pass liver metabolism. The syndrome varies depending upon the location of the tumor. Hindgut carcinoids are nonreactive while midgut tumors most often give rise to the classic syndrome. Foregut tumors, which include bronchial carcinoids often lack a decarboxylating enzyme and are associated with elevated levels of 5-hydroxytryptophan and rarely serotonin.[2] The APUD cell is plurpotential and can secrete an array of hormones, some of which are clinically silent. The enzyme kallikrein, secreted by the carcinoids and acting upon the serum proteins, produces bradykinins which are potent vasodilators implicated in the cutaneous flushing and wheezing[2] (Fig. 1). The various amines,

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Table 1

Carcinoids at MMC
1955-1978

Location	*Anatomical Distribution* MMC%	Other%	Ref.
Foregut			
Bronchus	31.8%	10.2, 14.1	(5)
Stomach	3.0	2.5, 1.9	(5)
Pancreas	1.5	0, 0.05	(5) (2)
Duodenum	1.5	3.0	(1)
Midgut			
Jejuno-Ileum	24.3	19.6, 25.2	(5)
Meckel's	1.5	2.3	(2)
Appendix	28.9	43.4	(5)
Hindgut			
Colon	1.5	6.0, 6.7	(5)
Rectum	3.0	15.8, 12.4	(5)
Ovary	1.5	0, 0.31	(5)
Unknown	1.5	— —	
Total #	67	1,867 & 970	(5)

Table 2

Bronchial Adenomas
MMC 28 Pts.
1955-1978

	MMC Number	Percent	*Other* Percent	Ref.
Carcinoid	21	75	51, 90	(7, 8)
Cylindroma	6	21	12, 60	(7, 8)
Mucoepidermoid	1	4	2, 3	(7)

their mechanisms of actions, and corresponding symptoms is beyond the scope of this article.

Bronchial Carcinoids

Carcinoid tumors are rare, occurring in 0.08 to 1.36% of reported autopsy series.[2] Bronchial carcinoids represent 0.6-8% of all primary tumors of the lung, the bronchogenic carcinoma being fifty times more common.[4,5] Our review of 67 carcinoids in all sites indicated a disproportionately higher incidence of bronchial tumors when compared to other anatomical locations and when compared to other studies (Table 1).

I *Incidence* (Table 2)

Bronchial carcinoids are grouped pathologically under "bronchial adenoma" and comprise the majority of this classification. The Maine Medical Center had a disproportionately higher incidence of bronchial carcinoids when compared to other anatomical sites but the same proportion as reported bronchial adenomas.

II *Age, Sex, Smoking* (Table 3)

The mean age of 52 of the MMC cases is slightly older than that of reported series.[9,10,11] The preponderance of females contrasts with other series but concurs with Weis' review of 14 patients in which a predilection for females was noted.[10,11] Smoking history was only elicited in approximately one-third of the patients, agreeing with other studies.[12]

Table 3

Bronchial Carcinoids
MMC 1955-1978

	MMC	*Other*
Mean Age:	52	43, 44, 48
Range:	15-77	13-92, 15-73
Sex:	66% F:34% M	46% F:54% M
		80% F:20% M
Smokers:	6 of 19 (31%)	7 of 28 (25%)

Table 4

Bronchial Carcinoids
MMC 1955-1978

	MMC No.	Percent	*Other* Percent	Ref.
Routine Chest X-ray	8/17	(57%)	11/27 (40%)	(12)
Symptoms:	16 Pts			
Dyspnea:	1	(6%)	4%, 5%	(9, 12)
Hemoptysis:	2	(12%)	42%, 45%	(10, 9)
Pneumonia:	3	(18%)	31%, 42%	(9, 10)
Cough:	3	(18%)	62%, 69%	(10, 9)
Chest Discomfort:	4	(25%)	21%	(9)
Asymptomatic:	6	(37%)	5%, 37%	(9, 10)
Duration of Symptoms:	8.8 Months (2D-2Y)			

Table 5

Bronchial Carcinoids
MMC 1955-1978

	Follow-up 7 to 183 Months *MMC* No.	Percent	*Other* Percent	Ref.
No Evidence of Recurrence:	20/21	(95%)	(87%,94%)	(10,5)
Regional Node Involvement:	3/21	(14%)	(6-30%)	(8)
Alive with Disease:	1			

III *Location*

This series showed approximately equal distribution between right and left lungs while some studies have shown a higher occurrence of lesions in the right pulmonary segments.[10,8] This study included two peripheral carcinoids not located in the endobronchial tree but in lung parenchyma.

IV *Symptoms and Diagnosis* (Table 4)

Eight of seventeen patients' lesions were discovered on a routine chest film; however, at MMC a significantly smaller percentage had hemoptysis than reported in other series. A larger percentage were asymptomatic and a significantly comparatively smaller number presented with either cough or pneumonia.

V *Extent of Disease and Treatment* (Table 5)

All were treated with lobectomy except for one total pneumonectomy. Follow-up had a range of seven to 183 months with a mean of 43 months. As indicated in Table 5, bronchial carcinoids are most often successfully treated with lobectomy and resection of regional nodes. To date, all of those patients with regional node involvement have shown no recurrence. Interestingly, one patient had elevated urinary 5-hydroxy-indole acetic acid after developing liver metastases approximately 60 months post-lobectomy.

Discussion

Luenec[10] is credited with the first recognition in 1831 of the bronchial carcinoid and Muller in 1882[6] was the first to describe the tumor. Not until the 1930's with the advent of bronchoscopy did Kramer establish the bronchial carcinoid as a clinical and pathological entity.[6] Because of their slow growth, contrasting with other pulmonary malignancies, they were categorized under the "bronchial adenoma," incorrectly implying benignity.

The histological classification of these lesions has been difficult. "Grade III-IV atypical" bronchial carcinoids are considered oat cell lesions and behave as such.[2] Our series included only typical bronchial carcinoids. Our records show no bronchial carcinoids before 1962 and during a six-year period from 1964 to 1972. The disproportionately higher number when compared to other anatomical sites and when compared to other studies is not explained except possibly by an increase in the volume of thoracic surgery done at this institution.

The high percentage of these malignancies found on routine chest x-ray is not surprising when one considers that a carcinoid in a small bronchus would stand out early while remaining clinically silent. However, the low incidence of hemoptysis in our series is most unusual. The highly vascular nature of these tumors is well appreciated and for this reason bronchoscopic biopsy should be avoided.[15] Cytology is unrewarding and only reported positive in approximately one-third of the cases.[14,12] The lower incidence of cough and pneumonia in our series may reflect the small number of patients in our series or perhaps the accuracy of the patient interviews. The duration of symptoms reflects either the acute onset with usually a cough or discomfort or a more chronic presentation with recurrent pneumonias associated with distal atelectasis secondary to an endobronchial lesion often with a "ball-valve" effect.

As reported in a few other studies,[12,7] smoking does not correlate with a high incidence of bronchial carcinoids which contrasts with the traditional association of other pulmonary malignancies with not only smoking but also maleness.

The syndrome is reported to occur in 2-7% of patients with bronchial carcinoids.[13] In the bronchial carcinoid syndrome, there are often severe and prolonged flushing and asthmatic attacks. Hyperther-

Continued on Page 405

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INDICATION Tenuate and Tenuate Dospan are indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use such as those described below.

CONTRAINDICATIONS Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result).

WARNINGS If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. *Drug Dependence* Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy* Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children* Tenuate is not recommended for use in children under 12 years of age.

PRECAUTIONS Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.

ADVERSE REACTIONS *Cardiovascular* Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System* Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache, rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal* Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic* Urticaria, rash, ecchymosis, erythema. *Endocrine* Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System* Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous* A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.

DOSAGE AND ADMINISTRATION Tenuate (diethylpropion hydrochloride): One 25 mg. tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg tablet daily, swallowed whole, in midmorning. Tenuate is not recommended for use in children under 12 years of age.

OVERDOSAGE Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phentolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product Information as of April, 1976

MERRELL-NATIONAL LABORATORIES Inc.
Cayey, Puerto Rico 00633

Direct Medical Inquiries to
MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215, U.S.A.

Licensor of Merrell®

References: 1. Citations available on request from Medical Research Department, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M.T., O'Dillon [Dillon], R.H., and Leyland, H.M. A comprehensive review of diethylpropion hydrochloride. In: Central Mechanisms of Anorectic Drugs, S. Garattini and R. Samanin, Ed., New York, Raven Press, 1978, pp. 391-404

Merrell

9 4672 (Y957A)

Overweight may not always be simple... complications can develop.*

Complicated or not...

Tenuate® Dospan® ©IV

(diethylpropion hydrochloride NF)

75 mg. controlled-release tablets



A useful short-term adjunct in an indicated weight loss program.

Overweight patients in certain diagnostic categories often require strict appetite control and a successful program of weight reduction may tend to diminish the incidence or severity of the complications in some patients. Diethylpropion hydrochloride has been reported useful in such patients and while it is not suggested that Tenuate itself in any way reduces the complications of overweight, it may have a useful place as a short-term adjunct in a prescribed dietary regimen. **Tenuate should not be administered to patients with severe hypertension; see additional Warnings and Precautions on the opposite page.**

In uncomplicated overweight.

Many patients, on the other hand, present with excess fat but no disease. While this condition is often termed uncomplicated obesity, complications of both a social and a psychologic nature may be distressingly real for the patients. In these cases, a short-term regimen of Tenuate can help reinforce your dietary counsel during the important early weeks of an indicated weight loss program.

Clinical effectiveness.

The anorectic effectiveness of diethylpropion hydrochloride is well documented. No less than 16 separate double-blind, placebo-controlled studies attest to its usefulness in daily practice.[1] And the unique chemistry of Tenuate provides "...anorectic potency with minimal overt central nervous system or cardiovascular stimulation."[2] Compared with the amphetamines, diethylpropion has minimal potential for abuse.

Tenuate—it makes sense. And it's responsible medicine.

*Studies have shown that obesity is associated with an increased incidence of hypertension, symptomatic heart disease, adult-onset diabetes, and other diseases.

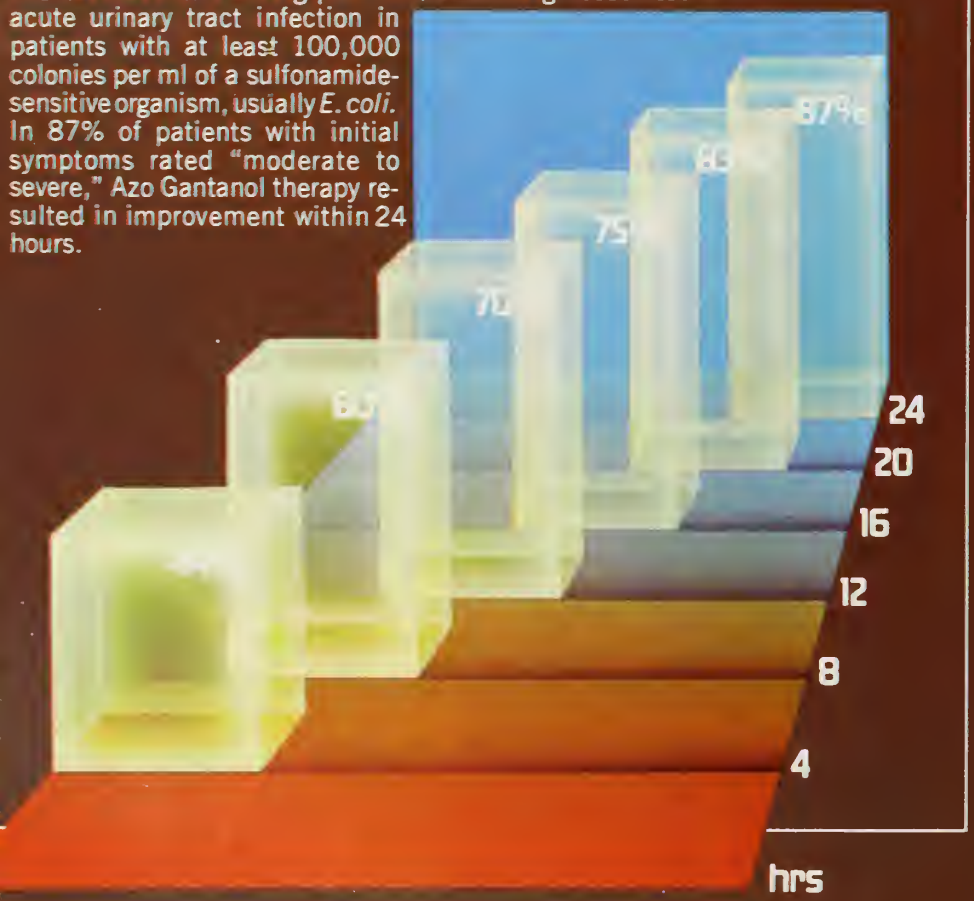
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For prescribing information see opposite page.

Important data on the pain of acute cystitis:

In 87% of patients studied [303 of 349], Azo Gantanol® reduced pain and/or burning within 24 hours*

A controlled, multicenter study assessed the efficacy of Azo Gantanol in relieving pain and/or burning associated with acute urinary tract infection in patients with at least 100,000 colonies per ml of a sulfonamide-sensitive organism, usually *E. coli*. In 87% of patients with initial symptoms rated "moderate to severe," Azo Gantanol therapy resulted in improvement within 24 hours.



Before prescribing, please consult complete uct information, a summary of which follows:

Indications: In adults, urinary tract infections complicated by pain (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organ (usually *E. coli, Klebsiella-Aerobacter, Staph coccus aureus, Proteus mirabilis*, and, less f quently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. **Note: fully coordinate *in vitro* sulfonamide sensitivi tests with bacteriologic and clinical response; aminobenzoic acid to follow-up culture medi increasing frequency of resistant organisms i the usefulness of antibacterials including su fonamides.** Measure sulfonamide blood level variations may occur; 20 mg/100 ml should maximum total level.

Contraindications: Children below age 12; su fonamide hypersensitivity; pregnancy at term during nursing period; because Azo Gantanol tains phenazopyridine hydrochloride it is con dicated in glomerulonephritis, severe hepatit uremia, and pyelonephritis of pregnancy with disturbances.

Warnings: Safety during pregnancy not estab Deaths from hypersensitivity reactions, agran tosis, aplastic anemia and other blood dysc have been reported and early clinical signs (throat, fever, pallor, purpura or jaundice) ma dicate serious blood disorders. Frequent CBC urinalysis with microscopic examination are ommended during sulfonamide therapy.

Precautions: Use cautiously in patients with paired renal or hepatic function, severe aller bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria stone formation.

Adverse Reactions: *Blood dyscrasias* (agran ulocytosis, aplastic anemia, thrombocytope leukopenia, hemolytic anemia, purpura, hyp thrombinemia and methemoglobinemia); *alle reactions* (erythema multiforme, skin eruptio Stevens-Johnson syndrome, epidermal necr urticaria, serum sickness, pruritus, exfoliati dermatitis, anaphylactoid reactions, periorbi edema, conjunctival and scleral injection, ph sensitization, arthralgia and allergic myocard *G.I. reactions* (nausea, emesis, abdominal hepatitis, diarrhea, anorexia, pancreatitis a stomatitis); *CNS reactions* (headache, perip neuritis, mental depression, convulsions, a hallucinations, tinnitus, vertigo and insomni *miscellaneous reactions* (drug fever, chills, nephrosis with oliguria and anuria, periarteri nodosa and L. E. phenomenon). Due to cert chemical similarities with some goitrogens, uretics (acetazolamide, thiazides) and oral h glycemic agents, sulfonamides have caused instances of goiter production, diuresis and glycemia. Cross-sensitivity with these agents exist.

Dosage: Azo Gantanol is intended for the ac painful phase of urinary tract infections. *Usu adult dosage:* 2 Gm (4 tabs) initially, then 1 (2 tabs) B.I.D. for up to 3 days. If pain pers causes other than infection should be sough After relief of pain has been obtained, cont treatment with Gantanol (sulfamethoxazole) be considered.

NOTE: Patients should be told that the oran dye (phenazopyridine HCl) will color the uri

Supplied: Tablets, red, film-coated, each co ing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 5

ROCHE

Roche Laboratories
Division of Hoffmann-La Roc
Nutley, New Jersey 07110

Fast pain relief plus effective antibacterial action

Azo Gantanol®

Each tablet contains 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl.

for the pain

for the pathogens

mia, hypotension, and oliguria may be present.[13] In some cases, the mitral valve may be more affected than the right sided lesions traditionally associated with gastrointestinal carcinoids and liver metastases.[13] Some authors propose that a bronchial carcinoid is not able to cause the syndrome without liver metastases because of the high concentration of pulmonary monoamine oxidase that degrades serotonin; however, although rare, this has been reported.[13] One patient in our series developed liver metastases with elevated 5HIAA urine levels approximately 60 months after lobectomy.

In spite of regional nodal metastases, prognosis was excellent in our series and in other reports. Distal metastasis, often to skin and bone with foregut carcinoids, involved the liver in only one case. Treatment of the pulmonary lesion includes lobectomy with regional node resection. The chances of discovering an elevated 5HIAA in patients with endobronchial carcinoids is small. However, if a patient has regional node metastases, follow-up with both chest x-rays and urine 5HIAA's is advisable.

Summary

The records of 21 patients with bronchial carcinoids at Maine Medical Center over a 23-year period revealed:

1. A disproportionately higher incidence than in other anatomical sites.
2. A significantly higher percentage of females.
3. An unusually lower presentation of hemoptysis, cough or penumonia.
4. A lack of association with cigarette smoking.
5. An excellent prognosis after resection even with regional node involvement.

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Posterior Fossa Arachnoid Cysts—*Continued from Page 401*

Acknowledgements

L. Reed Altemus, M.D. interpreted the CT scans, Russel C. Briggs, M.D. interpreted the RN scans and Carl A. Brinkman, M.D. performed the surgery on patient number two.

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Changing Needs of Surgical Training and Practice in Maine

RICHARD C. BRITTON, M.D.*

PERSPECTIVE

In 1947, when the surgical residency at the Maine General Hospital was initiated, all but a dozen of Maine's 437 towns and cities had fewer than 10,000 population and four-fifths of acute care hospitals in the state had fewer than 100 beds staffed by the majority of physicians practicing general surgery in the state. The curriculum was, accordingly, designed to fit this milieu and acknowledged the lack of qualified surgical subspecialists except in the larger towns and cities. The challenge was met by a program which differed from most university programs in having depth experience in orthopedics, urology, operative obstetrics, gynecology, and neurosurgery, Within a decade, two-thirds of the graduates were practicing in smaller communities and over half of their surgical activity was devoted to subspecialty care.

THE CHANGING SCENE

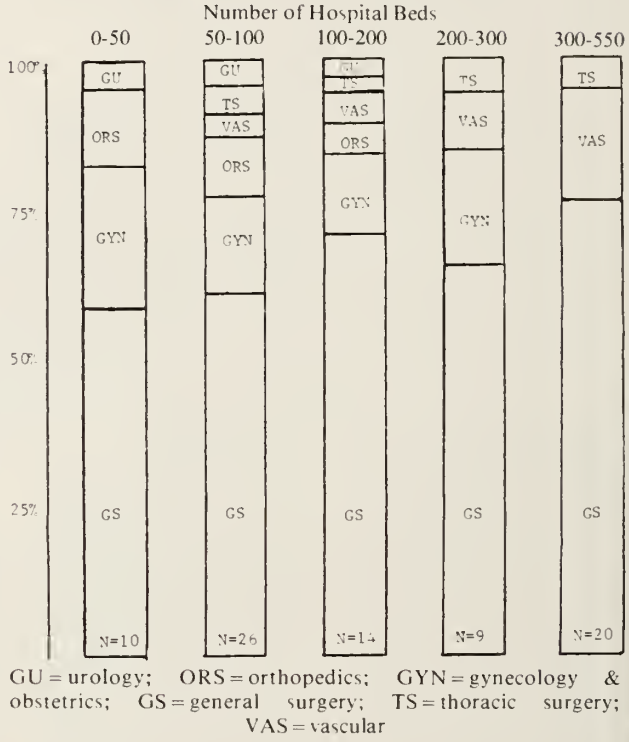
In 1968, a beginning change was perceived by Dr. Emerson Drake,[1] then program director, who surveyed graduates by questionnaire to elicit practice patterns and possible need for curriculum change. The forty-one replies indicated satisfaction with the broadly based training whether they entered practice in large or small communities or took advanced training. Suggestions were made for increased experience in thoracic, gastrointestinal, and vascular surgery. Confirming Drake's impression was evidence that increasing numbers of qualified specialists were entering practice in certain areas, thereby diminishing the role of the general surgeon in subspecialty care and the need for weighted specialty experience in training. This was most evident in areas with over 50,000 population, less so in areas with between 25,000 and 50,000 population, and least apparent in areas with under 25,000 population.

In 1973, a similar survey of graduates indicated a further decrease of significant involvement of general surgeons in orthopedic, gynecological, and urological surgery in communities with hospitals having more than 100 beds. Replies from graduates staffing hospitals with fewer than 50 beds and between 50 and 100 beds indicated continued involvement with subspecialty work in unchanged proportion to general surgery except in a few areas where it had decreased.

In 1978, a third survey also included all active physicians listed as practicing general surgery in the 1977 Roster of the Maine Medical Association. Of the 135 listings, 79 had completed a surgical residency and 62 were listed in the Directory of Medical Specialists as being certified. Table 1, using local hospital bed capacity as an indication of community size, summarizes the distribution of surgical practice effort averaged from 79 replies to the questionnaire. In the four hospitals with more than 200 beds, a few older surgeons continued the regular performance of orthopedic, urological, or gynecological surgery which constituted less than 25% of surgical activity. In the nine hospitals with between 100 and 200 beds, gynecological surgery continued to be a significant

TABLE 1

DISTRIBUTION OF SURGICAL PRACTICE



GU = urology; ORS = orthopedics; GYN = gynecology & obstetrics; GS = general surgery; TS = thoracic surgery; VAS = vascular

TABLE 2

PROFILE OF 36 GENERAL SURGEONS PERFORMING SPECIALTY OPERATIONS IN HOSPITALS WITH FEWER THAN 100 BEDS

	1968	*1978*	
		More than 5% of Practice	*Less than 5% of Practice*
Gynecology	100%	80%	11%
Fractures	100%	48%	32%
Urology	90%	14%	22%
Thoracic	7%	3%	5%
Vascular	13%	8%	19%

*From the Department of Surgery, Maine Medical Center, Portland, Maine 04102.

TABLE 3

*DISTRIBUTION OF SPECIALISTS BY COUNTY

	GS	FP GS	ANES	FP ANES	OBG	FP OBG	TS	OTO	PS	GU	ORS	FP ORS	IM	FP	NS
Androscoggin	11	1	7	—	9	2	1	3	1	2	6	—	18	10	2
Aroostook	7	6	2	3	3	2	1	1	—	2	2	—	9	13	—
Cumberland	25	2	17	1	20	—	8	7	3	6	10	1	64	34	4
Franklin	3	—	—	—	1	—	—	—	—	—	—	—	3	8	—
Hancock	4	—	1	—	1	—	—	—	—	—	—	—	6	10	—
Kennebec	15	4	5	2	8	—	4	4	—	2	7	1	32	15	4
Knox	6	—	3	2	4	—	—	2	—	1	2	—	9	11	—
Lincoln-Sag.	6	1	1	—	2	—	—	2	—	—	1	—	6	14	—
Oxford	4	3	1	1	1	1	—	—	—	1	2	—	5	20	—
Penobscot	15	1	6	1	8	1	4	4	—	3	10	—	31	23	3
Piscataquis	1	—	—	—	—	—	—	—	—	—	1	—	6	6	—
Somerset	3	1	2	1	1	—	—	—	—	1	1	—	4	8	—
Waldo	1	1	—	—	—	1	—	—	—	—	—	—	2	2	—
Washington	—	4	—	—	—	—	—	—	—	—	—	—	1	15	—
York	6	4	2	—	3	1	1	—	—	1	2	—	10	15	—

*Roster of membership of the Maine Medical Association, 1977.
GS = general surgery; FP = family practice; ANES = anesthesia; OBG = obstetrics & gynecology; TS = thoracic surgery; OTO = otolaryngology; PS = plastic surgery; GU = urology; ORS = orthopedics; IM = internal medicine; NS = neurosurgery.

portion of general surgical effort among both older and younger surgeons but urological and orthopedic surgery was still performed chiefly by older surgeons. In the fourteen hospitals with between 50 and 100 beds and the twenty hospitals with fewer than 50 beds, specialty surgery continued but represented less than half of surgical activity among the 36 respondents. Open and closed fracture reduction and gynecological surgery predominated with a few older surgeons continuing to do diagnostic cystoscopy and suprapubic prostatectomy. Replies recommended that new surgeons entering practice in those communities be capable of performing all forms of endoscopy, fracture management, gynecological, and vascular surgery. Of interest was the wider capability of Maine residency graduates in comparison with others.

Since the population indicated by the 1970 U.S. census has not changed the predominance of small communities and this study indicates that 46% of physicians practicing general surgery are located in communities with fewer than 100 hospital beds surgical training appropriate for such communities is of particular interest. Table 2 comparing specialty activity changes in the past decade indicates lessening need for weighted specialty training for all residents in certain specialties but continued need, especially in gynecology and fracture management, for those planning to practice in these communities. Our adaptation has been to maintain the intensity but reduce the length of rotations in orthopedics, gynecology, and urology in the basic program and to create additional elective rotations for further experience for graduates who plan to practice in smaller communities.

THE FUTURE

Although the diminishing role of the general surgeon in subspecialty surgical care may have, in some institutions, resulted from departmentalization and tightening of delineation of clinical privileges, the principle reason has been and is an accelerating migration of qualified specialists into both large and small communities in Maine. Table 3 indicates the distribution of specialists by county in 1977 and Table 4 indicates the availability of five specialty services within reasonable travel distance for patients living in communities having fewer than 100 hospital beds. These show the availability of specialists in gynecology, urology, and orthopedics within 50 miles, the exceptions being coastal Washington County and the northwest wilderness which are sparsely populated. Specialist services in thoracic, neurosurgical, plastic, and vascular surgery continue to be available only in larger communities.

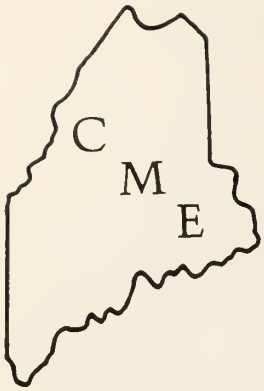
It seems likely that there will always be a need for well trained surgeons with broad specialty experience in many Maine communities and that this need will not be obviated by regionalization of less common, sophisticated, or costly surgical services. Respon-

Continued on Page 410

TABLE 4

AVAILABILITY OF SPECIALISTS IN MAINE
IN AREAS WITH FEWER THAN 100 BEDS

	Local	*Within 50 Miles*
Gynecology	51%	95%
Orthopedics	42%	90%
Urology	3%	90%
Thoracic	29%	79%
Vascular	33%	27%



CONTINUING MEDICAL EDUCATION IN MAINE

Conferences and Workshops

Title: **Interqual Program—Patient Care Audit Seminar—Basic and Advanced**
Date: October 22-23, 1979
Location: Airport Hilton, Bangor, Maine
Sponsor: Maine Hospital Association
Credit: AMA Category I—11 hours; AMRA—11 hours; AOA Category 2D—12 hours
Reg. Fee $165.00
For further information contact Margery Read; 622-4794

Title: **Symposium on Family Dynamics**
Date: December 1, 1979
Location: Portland, Maine
Sponsor: State of Maine Academy of Family Physicians
Credit: AAFP (prescribed)—3 hours
Symposium followed by Annual Business Meeting, Maine Chapter of American Academy of Family Physicians. For further information contact Roger E. Condit, M.D., Farmington, Maine, 778-6521.

Hospital Activities

Augusta General Hospital
Augusta, Maine

October 23, 1979 **Care of the Adolescent in the Hospital**
7:30-8:30 a.m. John F. Goodrich, M.D., AGH
This program has been certified AMA Category I and AAFP (prescribed). For further information contact Mrs. Nancy York; 623-4711. This program may be viewed over ITS.

Augusta Mental Health Institute
Augusta, Maine

Oct. 25, 1979	**Nursing Home Services** Nursing Home Unit, A.M.H.I.	10-11:30 a.m.
Nov. 1, 1979	**Clinical Problems Presented by Membership Cults**	10-11:30 a.m.
	Psychiatric Theory of the Mind in Relationship to the Cult Experience John G. Clark, M.D., Consultant in Psychiatry, Massachusetts General Hospital; Assistant Clinical Professor of Psychiatry, Harvard Medical School	1:30-3 p.m.
Nov. 8, 1979	**Forensic Services at AMHI: A Progress Report** Ulrich B. Jacobsohn, M.D., Clinical Director, A.M.H.I.	10-11:30 a.m.
Nov. 29, 1979	**Liability in the Clinical Setting**	10-11:30 a.m.
	Practical Legal Aspects of Mental Health Care Delivery James Vaccarino, J.D., Director of Legal Affairs, Massachusetts General Hospital	1:30-3 p.m.

The 10-11:30 a.m. Sessions are Grand Rounds; 1:30-3 p.m. Sessions are Inpatient Psychiatry Courses. All programs have been certified AMA Category I. For further information contact Pauline H. Soper; 622-3751.

Eastern Maine Medical Center
Bangor, Maine

Every Mon.	EEG Conference	12-1 p.m.
Every Mon.	Surgical Service—Chief's Rounds	5-6 p.m.
4th Mon.	ENT Section Meeting	12-1 p.m.
4th Mon.	Neurosurgery Section Meetings	4-5 p.m.
3rd Tues.	Dermatology-Pathology Conference	5-6 p.m.
3rd Tues.	Dermatology Section Meeting	6-7 p.m.
4th Tues.	Pulmonary Medicine Section Meeting	8-9 a.m.
1st Wed.	Hematology/Oncology Meeting	8-9 a.m.
Every Wed.	Tumor Clinic Conference	2-5 p.m.
Every Wed.	Radiology Conference (1) Ultrasound/Nuclear Medicine (2) Radiology Film Review (3) Neuroradiology (4) Teaching File Conference	5-6 p.m.
1st Thurs.	Ophthalmology Section Meeting	7:30-8:30 a.m.
	OB-GYN Conference (1) Pathology (2) GYN Analysis (3) OB-Pediatric Combined (4) In-Service and Education	8-9 a.m.
Every Thurs.	Pediatric Grand Rounds	9-10 a.m.
Every Thurs.	Medical Service Conference	10-11 a.m.
Every Thurs.	Cardiology Conference	11 a.m.-1 p.m.
2nd Thurs.	Orthopedic Grand Rounds	7:45-8:45 a.m.
4th Thurs.	Orthopedic Service Meeting	7:30-9 a.m.
4th Thurs.	Surgical Service Death Review	7:45-8:45 a.m.
Every Thurs.	Psychiatric Service Grand Rounds	10-11 a.m.
4th Thurs.	Urology Section Conference	7:30-8:30 a.m.
Every Fri.	Neurology Grand Rounds	8-9 a.m.

Visiting Professor Program:

2nd Thurs.	Medical Service Visiting Professor	10 a.m.-5 p.m.
2nd Thurs.	Anesthesia Service Visiting Professor	7-8 a.m.
3rd Thurs.	OB/GYN Service Visiting Professor	10 a.m.-4 p.m.
Saturdays	Surgery Service Visiting Professor	8 a.m.-Noon
4th Thurs.	Pediatric Service Visiting Professor	10 a.m.-5 p.m.
as scheduled	Orthopedic Service Visiting Professor	
as scheduled	Family Practice Visiting Professor	
as scheduled	Psychiatric Service Visiting Professor	
as scheduled	Radiology Service Visiting Professor	

All activities have been certified AMA Category I. For further informa-

Continued on Page 409

1980 Annual Session Site and Dates Selected - - -

June 12, 13, 14 and 15 are the dates to save on your calendar for the 1980 Annual Meeting of the Maine Medical Association. The site for the 1980 meeting will be The Balsams in Dixville Notch, N.H. Planning for the meeting is now under way. Scientific programs are being arranged by a committee under the direction of Dana M. Whitten, M.D.,of Belfast.

Check the Address - - -

Some mail is still being sent to the old MMA address. Delays in reply are often the result. Please remind your secretary of the new address and new office hours:

Maine Medical Association
524 Western Avenue
Augusta, Maine 04330 Telephone 622-3374

Office hours for the staff are 8 to 5 Monday through Thursday. On Fridays the office is occupied only by the Executive Director, and if he is absent - committee meeting, legislative hearing, or other Association business - the phone will not be covered. When finances permit, additional Friday coverage will be secured.

Members attending meetings at the new headquarters should look for a circular drive next to Trends Furniture store on Western Avenue (Route 202), approximately 9/10 of a mile west of the Augusta turnpike interchange. The building itself is a contemporary split level house with grey shingles, brick accent section and Cape Cod blue trim.

A Penny Saved? - - -

"A sudden flood of generic drugs that do not have Food and Administration approval entered the market in November of 1978 raising fears that pharmacists dispensing them will be exposed to serious legal risks." (Drug Topics 12/12/78)

"There are now large quantities of new generic, look-alike products on the market without F.D.A. approval, some of which are dissimilar in physical composition and therapeutic effect" - "use of the term *same* may be factually as well as legally wrong." (Drug Topics 4/20/79)

"The F.D.A. today warned patients who are taking prescription diuretic furosemide that three manufacturers have illegally marketed tablets that may be ineffective and therefore harmful to patients - F.D.A. recently received five reports of patients who became worse because Pharmadyne's version of the drug was not effective in removing fluid caused by their heart condition. Three of these patients were hospitalized as a consequence of taking the unapproved version of the drug." (H.E.W. News 3/30/79)

It appears that there are now quite a few non-F.D.A. approved look-alike generic drugs available in drug stores throughout Maine mimicking many name brand products such as Benedectin^{R}, Lasix^{R}, Tenuate Dospan^{R}, and Librax^{R}.

There are, of course, many F.D.A. approved generic drugs available and the non-approved drugs do not necessarily involve a violation of patent rights, only that these generics have not received the F.D.A. approval which documents their safety and efficacy.

There are safeguards available in Maine to physicians who would like to insure that their patients receive only F.D.A. approved generics or brand name products; i.e., check the box on the prescription form.

Attorney General Asked to Bring Suit - - -

Headlines in the October 1 Bangor Daily News said "Chiropractors want suit against 'boycott'". The article by Nancy Remsen of the NEWS staff then went on to say:

The Maine Chiropractic Association voted unanimously Saturday in Bangor to ask the state attorney general to consider an antitrust suit against the Maine Medical Association and others for "boycotting" and attempting to destroy the chiropractic profession.

Tim Dennis, president of the association and a doctor of chiropractic in Bath, said Sunday that he asked the membership to collect documentation of the alleged boycott by the medical profession to turn over to the attorney general's office.

"I feel confident that we have sufficient evidence available at the present time," Dennis said. He estimated that chiropractors and patients could supply "sufficient data within a week."

Many chiropractors face almost daily "harassment" and frustration because of the difficulty dealing with the medical doctors, hospitals, and laboratory facilities, Dennis said.

The effort by Maine chiropractors comes as a result of the successful launching of a suit this summer in New York by that state's attorney general. And Dennis said, the Maine Chiropractic Association has considered an anti-trust suit since five chiropractors in 1976 took on the American Medical Association, American Hospital Association, American Osteopathic Association, and numerous other physician subgroups.

Actions are also under way in New Jersey, Florida, Iowa, Illinois, Pennsylvania and Missouri, according to Moshe Myerowitz, vice-president of the association and a chiropractor in Bangor.

The proposed suit in Maine will probably focus not only on the problems which chiropractors and their patients currently face, but the history of "harassment." Myerowitz said.

"It goes back to 1972 when they attempted to delicense chiropractors," he said.

"There is no question but that there has been malice of forethought (sic), a pre-planned program to reduce competition and destroy chiropractic all over the country," Myerowitz said. Maine's attorney general "has no other choice but to follo through" with an antitrust suit.

tion contact Robert H. Brown, M.D., Chairman, Medical Education Committee; 947-3711, Ext. 330.

Henrietta D. Goodall Hospital
Sanford, Maine

Nov. 20, 1979 **"Advances in the Treatment of Diabetes Mellitus"**
Louis Bignati, M.D., Joslen Clinic, Harvard Medical School, Boston, Massachusetts

The meeting will be held at the Henrietta D. Goodall Hospital's Conference Room at 7 p.m. This program has been certified AMA Category 1. For further information contact Melvin Bacon, M.D.; 324-3632.

Maine Medical Center
Portland, Maine

Every Mon.	Student Technologist Conference	8 a.m.
Every Mon.	Hematology Pathology Conference	11 a.m.
Every Mon.	Pulmonary Conference	12 Noon
Every Mon.	Pediatric Residents Conference	1 p.m.
Every Mon.	Anesthesia Formal Resident Lecture	3:30 p.m.
Every Mon.	Surgical Pathology Review	4 p.m.
Every Mon.	Radiology Journal Club	5 p.m.
1st & 3rd Mon.	Clinical Nephrology Conference	11 a.m.
1st & 3rd Mon.	Hematology-Pathology Conference	12 Noon
3rd Mon.	Eye Conference	11:45 a.m.
Every Tues.	Radiology Residents' Seminar	7 a.m.
Every Tues.	Family Practice Grand Rounds	9 a.m.
Every Tues.	Electrocardiographic Interpretation	1 p.m.



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Every Tues.	Anesthesia Formal Resident Lecture	3:30 p.m.
Every Tues.	Surgical Seminar	4 p.m.
Every Tues.	Pathology Slide Seminar	4 p.m.
1st & 3rd Tues.	Radiology Pathology Conference	12 Noon
1st & 4th Tues.	Neurology Conference	12 Noon
2nd Tues.	Infectious Disease Conference	12 Noon
3rd Tues.	Hematology Conference	12 Noon
5th Tues.	Oncology Conference	12 Noon
Every Wed.	Radiation Therapy Conference	7 a.m.
Every Wed.	Urology Conference	7 a.m.
Every Wed.	Student Technologist Conference	8 a.m.
Every Wed.	Continuing Education Seminar	8 a.m.
Every Wed.	Medical Conference	9 a.m.
Every Wed.	Psychiatric Journal Club	12 Noon
Every Wed.	Cardiology Seminar	12 Noon
Every Wed.	Surgical Grand Rounds	5 p.m.
2nd Wed.	Guest Internist-Medical Conference	9 a.m.
4th Wed.	Medical Mortality Conference	9 a.m.
Alt. Wed.	Neurology-Psychiatry Seminar	11 a.m.
Alt. Wed.	Anesthesiology Journal Club	3 p.m.
Every Thurs.	Thoracic Surgery Conference	7 a.m.
Every Thurs.	OB/GYN Conference	7 a.m.
Every Thurs.	Anesthesiology Clinical Conference	7 a.m.
Every Thurs.	Diagnostic Radiology Teaching Conference	7 a.m.
Every Thurs.	Surgical Conference	8 a.m.
Every Thurs.	Pediatric Conference	9 a.m.
Every Thurs.	Tumor Consultation Board	11 a.m.
Every Thurs.	Medical Resident Conference	12 Noon
Every Thurs.	Surgical Seminar	4 p.m.
Every Thurs.	Endocrinology Conference	5 p.m.
Every Thurs.	Dental Specialty Lecture	6 p.m.
1st Thurs.	Anesthesia Mortality Conference	7 a.m.
1st Thurs.	Guest Pediatrician	9 a.m.
1st & 3rd Thurs.	Gastroenterology Conference	12 Noon
1st & 3rd Thurs.	Cardiac-Surgical Conference	12:30 p.m.
1st, 3rd, & 5th Thurs.	Pulmonary Physiology Conference	12:30 p.m.
2nd Thurs.	Cardiology Teaching Conference	12:30 p.m.
2nd Thurs.	Clinical Anesthesiology Lecture Series	3:30 p.m.
2nd Thurs.	Eye Staff Scientific Session	5:30 p.m.
2nd Thurs.	Maine Medical Center Medical Staff Meeting and Scientific Session	6 p.m.
2nd & 4th Thurs.	Pulmonary-Pathology Conference	12 Noon
2nd & 4th Thurs.	Endocrinology Conference	12 Noon
3rd Thurs.	Combined Guest Physician or Guest Surgeon Program	8 a.m.
3rd Thurs.	Clinical Anesthesiology Lecture Series	3:30 p.m.
4th Thurs.	Surgical Mortality Conference	8 a.m.
4th Thurs.	Anesthesia Mortality Conference	3:30 p.m.
Last Thurs.	Pediatric Mortality Conference	9 a.m.
Every Fri.	Thoracic Surgical Conference	7 a.m.
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Every Fri.	Medical Rehabilitation Staff Conf.	9 a.m.
Every Fri.	Orthopedic Conference	9 a.m.
1st Fri.	Dermatology Conference	12 Noon
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3rd Fri.	Rheumatology Conference	12 Noon
4th Fri.	Oncology Conference	12 Noon
Alt. Fri.	Oncology Radiation Conference	7 a.m.
Alt. Fri.	Gastroenterology Conference	10 a.m.

All programs have been certified AMA Category I. For further information contact Costas T. Lambrew, M.D.; 871-2111

Mercy Hospital
Portland, Maine

Nov. 1, 1979
7-8 p.m.

Electrical Stimulation of Fracture Healing
Seymour Zimbler, M.D.—Professor of Orthopedic Surgery—Tufts Medical School— Boston, Mass.

This program has been certified AMA Category I. For further information contact Harold Pariser, M.D.: 774-1461, Ext. 363

Mid-Maine Medical Center
Waterville, Maine

Oct. 25, 1979 — **Herniated Intervertebral Disc**
Jose M. Rodriguez, M.D., MMMC

Nov. 1, 1979 — **Sarcoidosis**
Irvin Paradis, M.D., MMMC
E. Osborne Coates, M.D., Togus VA Hospital, Augusta

Nov. 8, 1979 — **Visiting Professor—Tufts Medical School**

Nov. 15, 1979 — **Case Presentation—Family Practice Residents**

Nov. 29, 1979 — **Herpes Simplex Encephalitis**
Marvin Eisengart, M.D., MMMC
David Ginder, M.D., MMMC

All programs run from 12-1 p.m. and have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621. These programs may be viewed over ITS.

St. Mary's General Hospital/Central Maine Medical Center
Lewiston, Maine

Nov. 9, 1979
8 a.m.

Joint Grand Rounds—Central Maine Medical Center
Faculty from Tufts University School of Medicine

This program has been certified AMA Category I. For further information, contact Mrs. Phyllis Dube; 786-2901, Ext. 230.

Changing Needs of Surgical Training and Practice in Maine—*Continued from Page 407*

siveness to this need will continue as the guiding philosophy of those entrusted with the development of Maine's only general surgical training resource.

References

1. Drake, E.H.: Changing Educational Needs for Graduate Training of the General Surgeon. Amer. J. Surg. 119:362, 1970.

Letter To The Editor

To the Editor:

Re: Carbaryl R PAR

Introduction: How did a Newfoundland-based doctor become interested in Carbaryl?

Last year, the first full-scale operational spruce budworm forest spray program was initiated in Newfoundland. The chemical used was aminocarb (Matacil®), a carbamate-ester insecticide. Very little was known about this chemical and no books were written on it. Kuhr and Dorough's *Carbamate Insecticides: Chemistry, Biochemistry and Toxicology* (C.R.C. Press, 1976) had only the barest information on it. Thus, it was natural that comparisons would be made with carbaryl (Sevin®) and predictions made based on known carbaryl performance.

What is known about carbaryl is shocking.

Basis for Comparison: Both carbaryl and aminocarb are carbamate-ester insecticides used in the aerial spraying of fir and spruce forests against spruce budworm infestations. Maine uses mainly carbaryl. Over half of the published world literature on carbamate insecticides deals with carbaryl. When more is learned about aminocarb, of necessity more is learned about carbaryl.

Some Relevant Studies and Results:

1. Carbaryl is known to cause optic nerve degeneration and blindness in rats. Informal information from Japanese doctors suggests the possibility of the same effect in humans.
   M. Wakakura, T. Suzuki, S. Uga and S. Ishikawa, *Jap. Rev. Clin. Ophthal., 71* (5): 588 (1977).
   Rats fed carbaryl for 1 year developed optic nerve degeneration leading to blindness. Axon and myelin sheath degeneration was found.
2. Carbaryl is known to be teratogenic in high doses to guinea pigs.
   J. F. Robens, *Toxicol. Appl. Pharmacol., 15*, 152-163 (1969).
3. Carbaryl is known to be teratogenic in low doses to dogs.
   Pesticide-Wildlife Studies: A Review of Fish and Wildlife Service Investigations During 1961, 1962. U.S. Dept. of Int., F & W Service, Circ. 167 (1963).
4. Carbaryl is known to be teratogenic in low doses to mice.
   Report of the Secretary, Commission on Pesticides and their Relationship to Environmental Health, Parts 1 and 2, 10-11, 657-677, HEW, (Nov. 1969).
5. Carbaryl is fetotoxic to rabbits.
   J.F. Robens, *Loc. cit.*
6. Carbaryl is fetotoxic to cotton rats.
   G.W. Barrett, *Ecology, 49,* 1019-1035 (1968).
7. Carbaryl has been shown to cause neuroendocrine disorders, reduced fertility in both males and females and skeletal defects in the second generation in common rats.
   V.I. Vashakidze, *Soobach. Akad. Nauk. Gruz. SSR, 48,* 219-224 (in Russian).
8. Carbaryl causes birth defects in chickens.
   M. Ghadiri and D.A. Greenwood, *Tox. Appl. Pharm., 8,* (1966).
9. Carbaryl leads to reduced reproduction in bobwhites and pheasants.
   Effects of Pesticides on Fish and Wildlife: A Review of Investigations During 1960. U.S. Fish and Wildlife Service, Circ. 143 (1961).
10. *Carbaryl*, ingested at the same time as *sodium nitrite*, with the naturally occurring *hydrochloric acid* in mammalian stomachs causes the formation of *nitroso-carbaryl*, a highly mutagenic and carcinogenic chemical.
    a) R. Elespuru, W. Lijinsky, J.K. Setlow, *Nature, 247,* 386-387 (Feb. 8, 1974).
       This was the original report on nitroso-carbaryl mutangenicity.
    b) R.W. Rickard, H.W. Dorough, *Pharmacologist, 20* (3), 146 (1978).
       Nitroso-carbaryl formed in stomachs of rats and pigs, with more $N_a NO_2$ leading to greater amounts of the carcinogenic end product.
    c) W. Lijinsky, D. Schmahl, *IARC Int. Ag. Res. Cancer Sci. Publ., 19,* 495-501, (1978).
       Nitroso derivatives of six carbamate insecticides prepared (including nitrosocarbaryl) and fed to BD rats (0.4 mg/kg once/week x 10 weeks) and all six caused fore-stomach tumors.

Conclusion: It is inconceivable to me that a chemical could be allowed registration as a forest or as an agricultural spray today with the above studies published in the scientific literature. Certainly, when introduced in 1956 by Union Carbide, none of the above work had been performed and the requirements for pesticide registration were not as strict as they are today.

Therefore, the registration of *carbaryl* as a pesticide available for spraying should be revoked.

William Thurlow, B.A.(Chem.), M.D., F.R.C.S.(C)
Gander Medical Building
177 Elizabeth Drive
Gander, Newfoundland

Fall Meeting of the M.M.A. House of Delegates

Saturday, November 17, 1979

Mid-Maine Medical Center (Thayer Unit), Waterville, Maine

12:30 P.M.—Registration; 1:00 P.M.—Lunch; 2:00 P.M.—Meeting

9:30 A.M.—Meeting of the Executive Committee

Annual Meeting Dates For Your 1980 Calendar...

Maine Medical Association, June 12-15

The Balsams, Dixfield Notch, New Hampshire

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June 12, 13, 14, 15

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Stephens Memorial Hospital Issue

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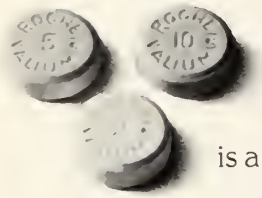
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The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication, abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d., alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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Exercise Testing as a Screening Procedure

What Happens to a Patient with a Positive Treadmill Exercise Test

William L. Medd, M.D., F.A.C.P.* and Shirley K. Gomez, R.C.T. **

Introduction

The literature is replete with articles discussing the value of treadmill exercise testing in predicting the presence of coronary disease. If one is to perform this noninvasive test, the terms sensitivity, specificity and predictive value need to be well-understood. Fortuin and Weiss[1] have written an excellent review dealing with all aspects of stress testing. They have reviewed many studies, and their article is an excellent resource for this field. Sensitivity for treadmill exercise testing (percent of patients with disease predicted correctly) varies between 54% and 84%. Specificity (ability of a negative test to correctly identify normal subjects) varies between 73% and 96%. This data comes from nine studies comparing the results of exercise testing and coronary angiograms in symptomatic patients. Despite the fact that exercise testing is not 100% reliable, one easily gains confidence from the literature[2,3] that it is the best noninvasive way to evaluate a patient for the presence of coronary disease. In addition, cardiac hemodynamics and arrhythmia may be studied.

Because a treadmill is a valuable diagnostic tool, one needs to evaluate the impact it has on patient care. A review of all the treadmills done in our hospital to see how this test affected long-term patient care was undertaken. We chose to follow-up the positive tests only as it would be easiest to obtain data on these patients. In addition, this group of people had the greatest chance of having coronary disease, and we were most interested in the role that a positive exercise test played in their care.

Methods

We reviewed every treadmill done at Stephens Memorial Hospital from October 1974, to February 1979. They were all done by one technician (S.G.) and interpreted by one of three physicians. The Bruce protocol or a modified Naughton protocol (see Table 1) was used for every test. An attempt was made to reach a submaximal to maximal heart rate. A test was considered positive if there was one millimeter or more of ST depression for at least .08 milleseconds. The interpretation was modified according to Selzers, et al[5] recommendations.

Table 1

Modified Naughton Protocol

Stage	*Elevation (% grade)*	*Speed (mph)*
1	0	1.0
2	0	2.0
3	3.5	2.0
4	7.0	2.0
5	11.5	2.5
6	15	3.0
7	17.5	3.0
8	20	3.5
9	20	4.0

All the patients were referred by one of twenty physicians. They all came to Stephens Memorial Hospital for the test. The population served was roughly 35,000 within a radius of fifty miles of Stephens Memorial Hospital. A questionnaire was sent to all the physicians to obtain data on every patient with a positive treadmill. This was followed up personally by a visit to the physician's office (S.G.) when there was any question about the patient's current status.

Results

From October 1974 to February 1979, 780 treadmills were performed on 707 patients (several patients had more than one exercise test) (see Table 2).

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TABLE 2

SUMMARY OF EXERCISE STRESS TESTS
(OCTOBER 1974 TO FEBRUARY 1979)

	Total	*Female*	*Male*
Number of treadmills	780	250	530
Negative treadmills	572	194	377
Positive treadmills	209	56	153
Number of patients	707		
Repeat treadmills	53		
two treadmills		11	27
three treadmills		3	11
four treadmills			2
six treadmills			1

TABLE 3

AGE DISTRIBUTION

Negative treadmills

	Female	*Male*
Average age	54.9	49.5
Youngest age	32	10
Oldest age	79	80
Mean age	55.5	45

Positive treadmills

	Female	*Male*
Average age	59.4	56.7
Youngest age	34	30
Oldest age	77	78
Mean age	55.5	54

TABLE 4

POSITIVE TREADMILL DATA

Positive treadmills	209
Repeats	26
Total patients	183
females	51
males	132
Patients found for follow-up	169 (92% of total)
Patients actually located	169

There were 571 negative treadmills and 209 positive treadmills. The age of the patients with negative tests and positive tests is presented in Table 3. The average age of the females with negative exercise tests was 54.9 years compared to the males who averaged 49.5 years. Predictably, the ages of the males and females with positive tests was greater with the average female age being 59.4 years and the male age being 56.7 years. The duration of follow-up varies from 52 months to one month, with an average of twenty-two months (Table 4).

An attempt was made to obtain data on the current status of all patients with positive treadmill stress tests. The following questions were asked: were they 1) alive or deceased? 2) what was their level of activity? 3) what were their current medications? 4) did they have coronary angiograms? 5) had they undergone coronary bypass surgery? Of the 209

Continued on Page 417

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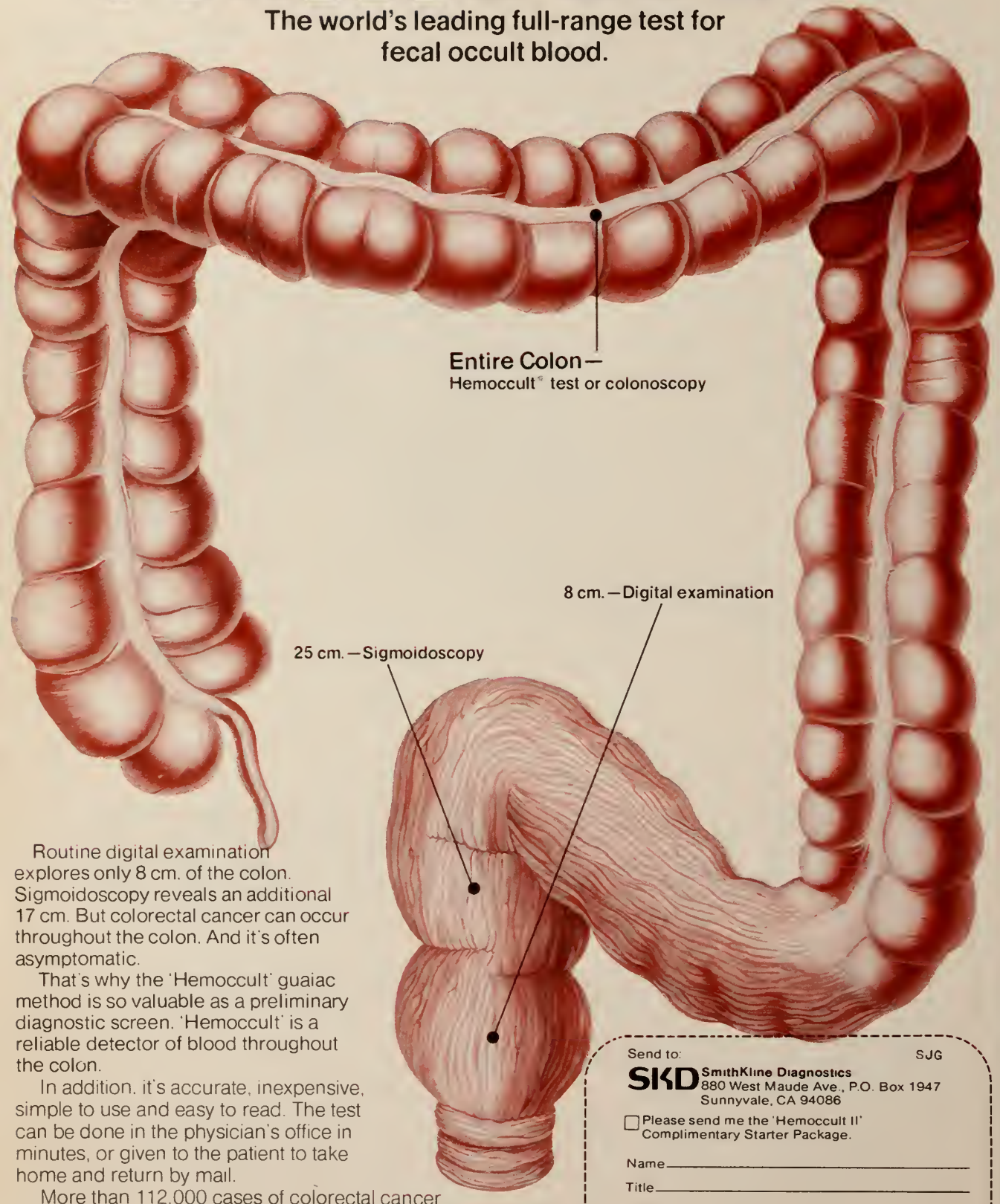
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positive treadmills, 26 tests were repeated on the same patient. This left a patient population of 183 patient to follow-up. There were 51 females and 132 males. We were able to obtain follow-up data on 169 patients, or 92% of the total population (Table 5).

TABLE 5

CURRENT STATUS OF PATIENTS WITH POSITIVE TREADMILLS

Deceased	4 (1.9% of total patients with 22 months of follow-up) one 40-year-old male—suicide one 70-year-old male—LVA one 75-year-old male—unknown one 69-year-old male—suicide		
Level of activity			
	Active (minor chest pain)		61
	Moderately active (Limiting angina)		76
	Inactive (chest pain that limits activity)		31
Patients on medication			
	Propranolol		124 (68%)
	Longacting nitrites		unreliable data
Patients who underwent coronary angiography			
	Total	*Males*	*Females*
	20 (13% of patients)	15	5
Patients who underwent bypass surgery			
	Total	*Males*	*Females*
	14 (7.6% total)	10	4

Of the 169 people followed up (average 22 months from exercise test to date of follow-up), only three were deceased and only one of these could have died from coronary disease. All but 31 of these patients were leading an active or moderately active life. Of note was that 68% of all patients with a positive treadmill were taking a beta blocking agent in the form of propranolol.

Table 6 summarizes the catheterization data. Thirteen percent of the 183 patients underwent cardiac catheterization. One patient had minimal disease; one patient had an A-V fistula; another had a normal catheterization. Two other patients had catheterization, but the results were not obtainable. The remaining 14 people had catheterization and coronary bypass surgery. This constitutes 7.6% of the 183 patients. Eight of the 14 patients who had bypass surgery are taking propranolol. Also, four out of five patients who didn't undergo bypass surgery are on propranolol.

DISCUSSION

This retrospective review was undertaken to answer the question of what happens to a person with a positive treadmill exercise test. Does this isolated test have predictive value with regard to longevity? Does everyone with a positive test have coronary catheterization and end up with bypass surgery? Do all these patients end up on medication? Does this test economically benefit the patient?

TABLE 6

RESULTS OF CARDIAC CATHETERIZATION

Date of treadmill	*Patient*	*Angiogram*	*Bypass*	*Medications*	*Follow-up*
4/77	F 46	Yes (mild disease)	No	Inderal®	22 months
2/78	M 63	Yes (5-vessel disease)	Yes	Inderal	12 months
3/78	F 58	Yes	Yes	Inderal Isordil®	11 months
1/79	F 62	Yes	Yes	Inderal Thyroid B/P med.	4 months
1/79	M 46	Yes	Yes		4 months
8/77	M 57	Yes	Yes	Inderal	18 months
2/79	M 56	Yes (normal)	No	Inderal Nitro®	3 months
8/75	F 75	Yes	Yes	Inderal Pacemaker	42 months
9/78	M 47	Yes (A-V fistula)	No	Nitro	5 months
6/76	M 54	Yes (unknown)	No	Inderal Nitro	32 months
1/78	M 57	Yes (unknown)	Yes	Inderal Nitro	14 months
3/78	M 55	Yes	Yes		8 months
12/77	M 61	Yes	No		18 months
11/78	F 72	Yes	Yes		4 months
1/77	M 52	Yes	Yes		25 months
3/76	M 62	Yes	Yes		35 months
7/76	M 47	Yes	Yes (4/79)	Inderal	
9/76	M 46	Yes	Yes	Inderal	29 months
3/76	M 60	Yes	Yes		35 months

We have answered some of these questions. The study would have been enhanced if we had data on the negative tests. Our data is not as extensive as that reported by Elestead and Wan[6]. They reported a follow-up series consisting of 2,700 patients out of 8,000 from their medical center. They dealt with coronary events and death and the reliability of the exercise tests in predicting these occurrences. Our follow-up was less extensive, but we were trying to answer some very specific questions.

We obtained good follow-up with data obtained on 88% of our study population. There was only one death which could have been related to coronary disease. Although our follow-up averaged only 22 months, this still is an interesting result, indicating that a positive treadmill doesn't lead to a high risk of death in the immediate future. We did not obtain data on coronary events other than death, but judging from the patients' level of activity, they are all leading near normal lives.

A large number of our population with positive tests were taking propranolol. This could represent one factor influencing the improved outlook for this group. In addition, one needs to consider the role of coronary artery bypass surgery in the treatment of people with positive treadmills. Certainly from our data a positive exercise test does not immediately lead to cardiac catheterization. In fact, only 20 out of 183 patients underwent cardiac catheterization. From that group only 14 patients underwent coronary artery bypass surgery.

Economics plays more of a role in our medical lives everyday. There is great reluctance for third party payers to reimburse doctors and hospitals for an exercise test. In fact, Blue Cross and Blue Shield of Maine will not pay for treadmills, thus forcing the patient to pay. Despite the fact that physicians know patients have to pay for stress testing, the test remains crucial, as it is a valuable tool in managing patients with coronary disease and evaluating patients with chest pain. The data presented supports the use of exercise testing as an economic way of managing these patients. It certainly helps patients to obtain medical therapy, e.g., 118 patients on beta blockers. Possibly this is a reason why these people have a low death rate and spend less time in the hospital. Finally, it is sobering to realize that 209 treadmills at $80.00 per test cost $16,720 or about the cost of one coronary catheterization and bypass operation. In fact, the cost of all the treadmills, which equals $62,400, would have equalled approximately the cost of four cardiac catheterizations and bypass operations. Perhaps it is more cost-conscious to pay for a test of proven efficiency that leads to improved patient care and less time in the hospital.

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1. Fortuin, N.J., Weiss, J.L.: Exercise Testing. Circ 56:699, 1977.
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Continued on Page 427

Tablets

PERCOCET®-5 (II)

Brief Summary of Prescribing Information

DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS

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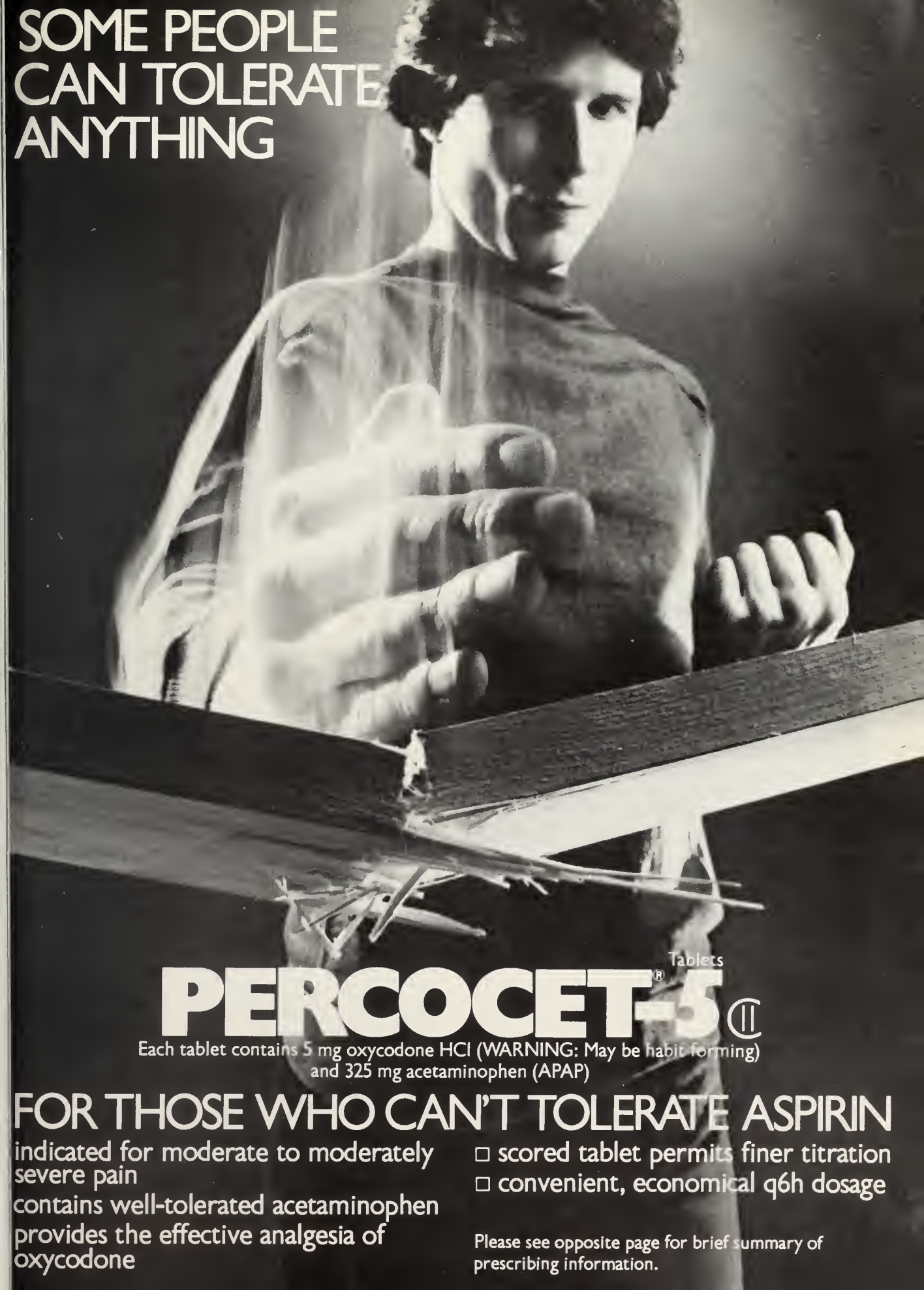
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Left Ventricular Aneurysm

Report of 144 Cases and Review of the Literature

MICHAEL A. LACOMBE, M.D., F.A.C.P.* AND PAUL N. YU, M.D., F.A.C.P., F.A.C.C.**

The study of left ventricular aneurysms is clouded by considerable inconsistency of definition. Were left ventricular aneurysms now only of academic interest, one might allow those interested in the subject to become embroiled in a battle of definitions without further argument. There are, however, pragmatic concerns. The five-year survival of a patient with left ventricular aneurysm is no better than the patient with ovarian carcinoma. Surgical resection of the aneurysm vastly improves survival,[1] but the surgery may endanger those who have left ventricular scars, infarcts, or dyskinetic myocardium. It would be better for us to know the difference. Indeed, resection of a left ventricular aneurysm as opposed to enhanced perfusion of a scar containing viable myocardium are two quite different modes of therapy.

A better definition of terms might also give us a more consistent idea of morbidity and mortality from left ventricular aneurysm. Past extensive reviews have differed widely in the very important area of prognosis. Some authors[2-4] have recently argued for the strict, classical definition of left ventricular aneurysm proposed by Edwards:[5] "A protrusion of a localized portion of the external aspect of the left ventricle beyond the remainder of the cardiac surface, with simultaneous protrusion of the cavity as well."

Such strict criteria will eliminate healed infarcts with scarring, some thinning, but no deformity of contour, as well as areas of dyskinesis (paradoxical motion), akinesis (no motion), asynergy (no synchronous motion), and other mechanical abnormalities of wall motion, from the realm of left ventricular aneurysm. By definition, the diagnosis of cardiac aneurysm will then only be made postmortem, or at surgery, and then sometimes only with the help of epicardial electrocardiograms and negative intraluminal pressure in the left ventricle.[3]

There is one further argument for the use of strict criteria proposed by Edwards. There is some good laboratory evidence that ventricular aneurysms produce their mechanical disadvantage (i.e., by loss of contractile tissue) quite differently than do acute infarcts (i.e., by loss of contractile tissue and by significant paradoxical systolic expansion).[6] In short, aneurysms behave differently in a mechanical sense than do myocardial scars.

It is the purpose of this paper to review retrospectively 144 cases of left ventricular aneurysm and to review critically the literature dealing with cardiac aneurysm.

Materials and Methods

Autopsy records from Strong Memorial Hospital for the period of 1935 to 1970 were reviewed, and 130 cases of left ventricular aneurysm identified. Fourteen additional surgical cases were also studied. Telephone follow-up was done on the surgical cases. All records were subjected to data analysis, which forms the body of this paper. For data analysis of myocardial infarction, data retrieval of 1642 cases from 1965-1970 was done.

An extensive review of the literature found only three other clinicopathologic reviews of left ventricular aneurysm, totalling 146 cases[7-9] in which the Edwards' criteria was strictly adhered to. In the surgical literature, an additional 46 cases in six small series fulfilled the criteria.[2,10-14] Perhaps equally important, a large number of series, both surgical[1,15-32] and non-surgical[33-45,51] not fulfilling the Edwards' criteria, were identified and reviewed.

Incidence

During the period of 1965-70 when data could be retrieved, we found 70 cases of left ventricular aneurysm per 1642 cases of myocardial infarction, for an incidence of 4.25%. Dubnow's[7] figures were 80 per 2293 (3.5%) and Berman's[8] were 18 per 192 (9.4%). Summing these results yields an incidence of aneurysms from myocardial infarction of 4%. Our autopsy incidence was 0.6%, and Dubnow's 0.74%. Mean age was quite similar for our study and for the other three,[7-9] being 63, 67, 66, and 63 years respectively. The male:female ratio for our study was 3:1, and when all four studies were combined, 73% of the cases were male.

Pathology

Most ventricular aneurysms involve the apex or anterior wall of the left ventricle, or both. Posterior aneurysms are quite uncommon, and right ventricular aneurysms decidedly rare. Why the former should be uncommon has been a matter for discussion in the past. Some[46] have proposed that the richer collateral circulation from the right and left circumflex arteries supplying the posterior surface makes aneurysm formation less likely. Others[41] cite the more lethal nature of posterior infarcts, which may involve conduction tissue or papillary muscle and thus prevent the patient from living to develop an aneurysm. In Dubnow's study, 79% involve the anterior wall, 61% the apex, and 19% the posterior wall. Table 1 summarizes our findings (please note

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TABLE 1

LOCATION OF ANEURYSM
(N = 144)

Anterior Wall (78/144 = 54%)	
Alone	29 — 20%
With septum	10 — 7%
With apex	24 — 17%
With apex and septum	12 — 8%
With second aneurysm	3 — 2%
Apex (76/144 = 54%)	
Alone	23 — 16%
With anterior wall	24 — 17%
With posterior wall	7 — 5%
With septum	6 — 4%
With right ventricle	1 — 1%
With anterior wall and septum	12 — 8%
With second aneurysm	3 — 2%
Posterior Wall (24/144 = 17%)	
Alone	17 — 12%
With apex	7 — 5%

(Note: Percentages based on N = 144)

TABLE 2

ASSOCIATED CORONARY OCCLUSION
(GREATER THAN 50% NARROWING; N = 144)

Less than 50% narrowing	12	8%
Left anterior descending	101	70%
Alone	24	17%
With circumflex	12	8%
With right coronary	12	8%
Three vessel disease	53	37%
Left circumflex	66	46%
Alone	0	0%
With LAD	12	8%
With RCA	1	1%
With LAD and RCA	53	37%
Right Coronary Artery	73	51%
Alone	7	5%
With LAD	12	8%
With LCA	1	1%
With LAD AND LCA	53	37%

that percentages exceed 100% because of overlapping categories). We found three cases of 144 with two aneurysms, and a single case (not represented on the table) of aneurysm of the right ventricle alone. Right ventricular aneurysms are distinctly unusual and associated with causes other than coronary artery disease.[67] We saw no instances of atrial aneurysm in our series, though these have been reported.[68-69]

The location of associated coronary artery occlusion is shown in Table 2. Note the predeliction for left coronary artery disease in patients with aneurysm and the high incidence (37%) of three-vessel disease. Figures 1 and 2 show the coronary arteriograms of patient B.D., who subsequently underwent resection of a large antero-apical aneurysm.

The incidence of calcified aneurysms in our series was 13%, compared to 12% and 11% for Berman's and Dubnow's series respectively. In cross-tabulating our 19 patients with calcified aneurysm against infarct-death intervals, the previously reported good



Fig. 1. Coronary Angiogram of B.D.—Severe narrowing at origin of LAD.



Fig. 2. Patient B.D.—Severe narrowing of circumflex.

prognosis for those patients was borne out. Calcified aneurysms should be left alone.

Pericarditis occurred in 42% of our patients and had no bearing on prognosis. Mural thrombi were present in 60% of our series; the incidence in the four series combined was 57%.

CLINICAL FEATURES

To develop an aneurysm, a patient must have severe coronary disease, yet survive his infarct. Cer-

Table 3

Associated Diseases
Post-infarct patients (N = 1642) vs. aneurysm patients (N = 144)

	Post-M.I.	*Aneurysm*
Congestive heart failure	23%	86%
Cardiogenic shock	2%	22%
Diabetes mellitus	24%	23%
Hypertension	27%	28%
Valvular disease	4%	30%
Lipid abnormalities	2%	12%

Table 4

Direct Cause of Death
(N = 144)

CHF	44	31%
Acute M.I.	18	13%
Thrombo-embolism	11	8%
Sudden death or arrhythmia	27	19%
Post-op	3	2%
Rupture	3	2%
Endocarditis	1	—
Non-cardiac	25	17%
Living	11	8%

tain other risk factors, such as valvular heart disease, hypertension, and subsequent infarction undoubtedly then play a role in the etiology of cardiac aneurysm. In fact, only one of our cases resulted from a cause other than coronary artery disease—in a patient with endocarditis during the pre-antibiotic era. Lack of adequate convalescence in patients during the infarct period has been cited as a possible cause for aneurysm formation. Dog experiments support this theory.[43] Corticosteroids given for Dressler's syndrome have also been implicated in causing aneurysms through poor healing.[47] In our series no patients received corticosteroids, but a strikingly high 19% either left the hospital within a week after infarction or had suffered an undiagnosed infarct.

Sternberg[48] described the four stages in the development of an aneurysm as angina, infarction with pericarditis, latent period, and aneurysm formation leading to congestive failure, sudden death, or both. Our patients had a high incidence of angina (56%) and of congestive heart failure (86%), and a relatively high incidence of sudden death (19%) not previously reported. The congestive failure was typically severe and refractory to medical management—22% of patients went on to cardiogenic shock. Table 3 compares the incidence of certain diseases in aneurysm patients with post-infarction patients. Because Schlicter[33] had reported an incidence of 25% of gallbladder disease in aneurysm patients, we looked at this also—and found an incidence of 33%. We have no explanation for this. Systemic emboli occurred in 53 patients (37%), but 16 patients *without* a mural thrombus had embolic episodes. Ventricular arrhythmias were common: 43% had frequent premature beats, with 24% having episodes of ventricular tachycardia and 16%, ventricular fibrillation. Ventricular arrhythmias as a sequella of cardiac aneurysm are a common problem.[70-71] These arrhythmias are often refractory to medical management, although they may be amenable to surgical treatment.

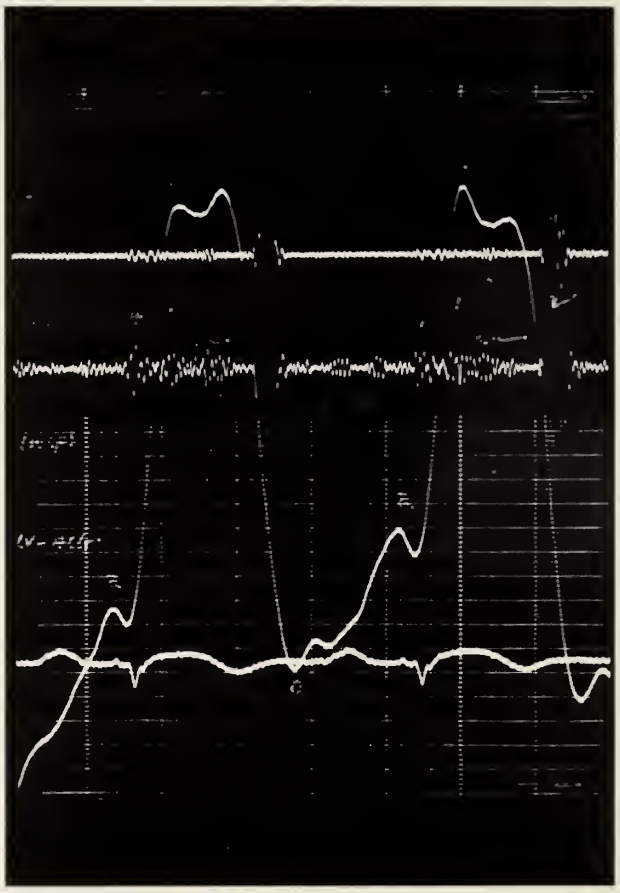


Fig. 3. B.D.'s apex cardiogram shows graphically precordial dyskinesis.

Left ventricular aneurysm carries a poor prognosis. The majority of our cases were debilitated with either congestive heart failure, angina pectoris, or both. Only 22% of the patients lived beyond five years from the time of infarct. About three-fourths had congestive failure as their chief or contributing cause of death. Table 4 gives the data on the chief cause of death in our series. Note the high number of patients dying suddenly, or from documented arrhythmia. In cross-tabulating the data, we found no statistically significant relationship between location of aneurysm and infarct-interval nor between location and cause of death, except that all three patients dying from rupture had apical aneurysms.

Diagnosis

There are no cardinal findings on physical examination which will make a definitive diagnosis of left ventricular aneurysm. The presence of a double precordial impulse, a soft first sound, a third heart sound, a forceful, "rolling" dyskinetic precordium

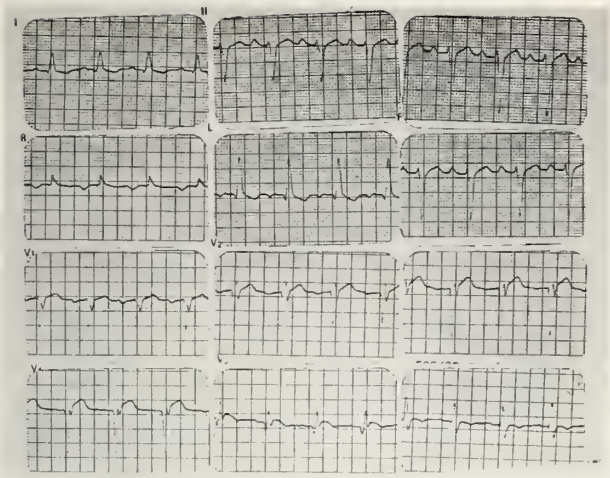


Fig. 4. EKG of B.D. illustrates persistent ST elevation, Q1T1, SIISIII, and Goldberger (R-AVR) patterns.

with a weak pulse in a patient with severe heart failure or refractory angina should make one suspicious, however. Figure 3, the apex cardiogram of patient B.D. demonstrates the double apical impulse of ventricular aneurysm. In one-half of our cases, a soft S-1 and an S-3 were described, one-fifth had mention of an abnormal apical impulse, and in 14% the diagnosis was suggested after physical examination.

Other workers[39,42,49,50,60] have discussed in detail the electrocardiographic abnormalities associated with ventricular aneurysm. In brief, these are patterns suggesting intraventricular conduction delay (Q-1, T-1, S-2, S-3 patterns), Goldberger's sign (R-AVR), and persistent S-T segment elevation. Figure 4, B.D.'s EKG, illustrates these changes. One-fourth of our patients had some form of intraventricular conduction delay, 44% had persistent S-T elevation, and only 23%, Goldberger's sign. When corrected for location of aneurysm, these figures didn't improve much; only one-half of the anterior and apical aneurysms had S-T elevation. A rather dismal statistic came to light—the diagnosis was suggested on serial EKG's only 12% of the time—too frequently patients with angina, aneurysm, and S-T segment elevation were readmitted to coronary care units on acute infarction protocols.

When is "persistent" S-T segment elevation persistent? Gorlin and associates state that S-T elevation present longer than two weeks post-infarction is considered persistent.[49] Patients in Gorlin's study who had persistent S-T elevation also had higher levels of serum creatine phosphokinase and had an advanced degree of asynergy. Persistence of S-T elevation as an indicator of asynergy may explain why some of our patients continued to have persistent S-T elevation after resection of their aneurysm. A final note on the electrocardiogram in wall motion abnormalities: Gorlin[45] and Helfant[52] have emphasized the predictive value of pathologic Q waves in recognizing asynergy.



Fig. 5. B.D.'s plain chest plate shows deformity of cardiac contour.



Fig. 6. A somewhat more obvious deformity of the cardiac silhouette.

The routine chest roentgenogram is a notoriously poor tool for diagnosing ventricular aneurysm. Although the examples in Figure 5 (patient B.D.) and Figure 6 are rather obvious, only 15% of our cases showed any deformity of cardiac contour and only



Fig. 7. B.D.'s ventriculogram showing large aneurysm of apex—and anterior wall.

6% demonstrated calcified aneurysm on x-ray films. Fluoroscopy doesn't improve matters much; of 49 cases fluoroscoped, only 29% showed abnormal pulsations.

Conventional M-mode Echocardiography often misses the inferior, lateral, and apical portions of the heart. For detecting abnormalities of wall motion (and thus increasing suspicion of an aneurysm) cineventriculograms,[53-56] radarkymography,[57] and gated scintiphotographs[58-59] have offered the best results. Left ventricular cineangiography is the diagnostic tool against which other, noninvasive techniques, are measured. Its chief disadvantage, aside from being an invasive procedure, is that patients cannot be followed sequentially. Also, cineangiography usually demonstrates a wall motion disturbance and only infrequently shows us an unequivocal aneurysm (see Figure 7). One patient in our series showed on ventriculogram akinesis of the anterior, lateral, and apical surfaces, with no dyskinesis, and later at autopsy had an aneurysm involving only the apex. Radarkymography scans the heart image on a television monitor and tracks the motion of the heart border. Intracardiac blood pool scintiphotographs, using 99-Tc-m, and taken in end-systole and end-diastole, offers the best noninvasive technique for evaluating left ventricular motion mechanics and for following patients at high risk for developing aneurysms.

Surgery

Surgeons have been resecting ventricular aneurysms for the past thirty years. In early reports[10-13] fulfilling the Edwards' criteria, two of 20 patients did not survive the postoperative period. In two recent large series,[1,15] totalling 500 patients, the operative mortality was 9.8% and 7% respectively,

Continued on Page 425

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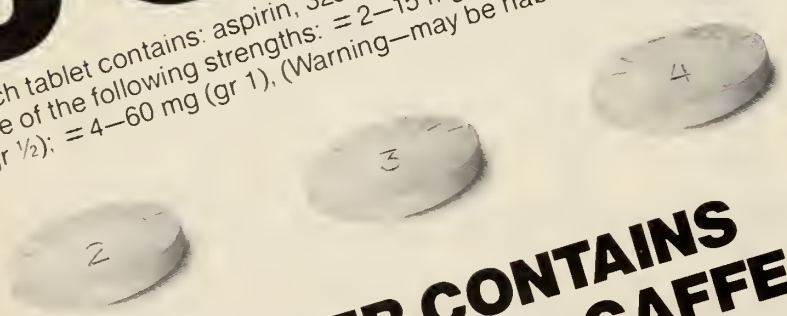
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Fig. 8. Patient B.D. at surgery.



Fig. 9. B.D.'s post-op ventriculogram.

and the five-year survival for both, about 75%. While these are optimistic figures, they do need to be tempered somewhat. In the series of 400 aneurysmectomies done at the Cleveland Clinic,[1] 174 patients also had valve operations or revascularization procedures done. Although the in-hospital mortality for those having aneurysmectomy alone was at 9% as well, the five-year survival for this group is not available from the figures given in this paper. Revascularization has undoubtedly had a salutary effect on mortality as well as upon relief of congestive heart failure, angina, and ventricular tachycardia, the three primary indications for surgery.

A second objection to these mortality figures turns on our difficulty with definition. While "only thinned-out transmural scars that have completely lost their trabecular pattern" were resected, "the

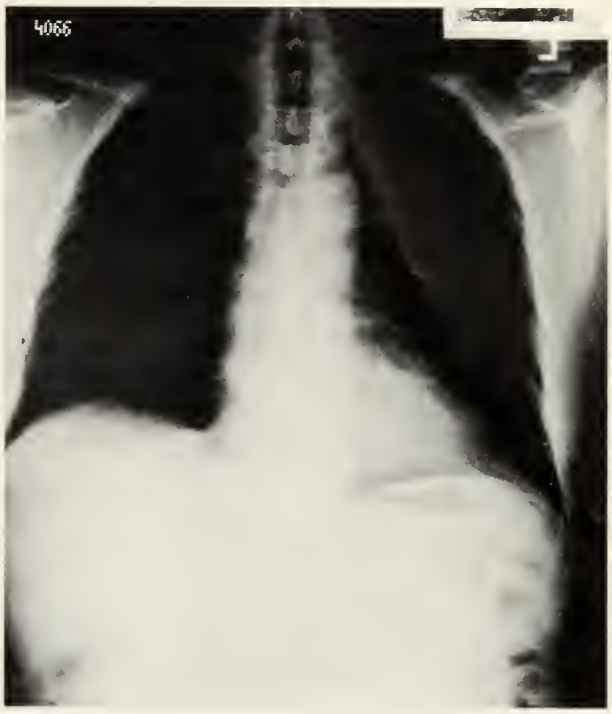


Fig. 10. B.D.'s post-op chest plate.

aneurysm did not always bulge outward."[1] Were these then pure aneurysms? It is hard to imagine a 2 x 2 centimeter ventricular scar compromising seriously ventricular mechanics. We do have some notion of how much ventricular area needs to be involved to impede ventricular performance, i.e. about 20-25%.[34] Perhaps in patients with small scars, revascularization procedures alone might have served as well.

In a series of 23 aneurysmectomies, where the Edwards' criteria was adhered to and argued for, the operative mortality was 22%.[2] All five of the in-hospital deaths had dyspnea at rest, as opposed to only two of the other 18. The time between infarct and surgery was shorter, as was the interval between infarct and the onset of symptoms—an important point to consider when selecting patients for surgery.

Although the bulk of surgical candidates will have refractory congestive heart failure, angina, or both, patients with refractory ventricular tachyarrhythmias may also profit from aneurysmectomy.[18,61-66] When recurrent ventricular tachyarrhythmias threaten a patient, ventricular aneurysm should he suspected; 19% of our patients died suddenly. Another indication for aneurysmectomy is the patient with systemic emboli and suspected aneurysm. In this instance, anticoagulants are of no benefit.[4]

Figures 8-10 show B.D. at surgery and show his postoperative ventriculogram and chest film.

Summary and Conclusions

The key points in this review of ventricular aneurysm are:

1. The incidence of aneurysm developing after

myocardial infarction is about 4%.

2. Aneurysms predominate in males by a ratio of 3:1.
3. Most aneurysms involve the anterior and apical walls of the left ventricle.
4. Ventricular aneurysm is associated with severe coronary artery disease.
5. A calcified aneurysm indicates a good prognosis.
6. Ventricular aneurysm itself implies a poor prognosis with a five-year survival of about 20%.
7. Congestive heart failure, often severe, is common in these patients.
8. Systemic emboli are common, and anticoagulants do not help.
9. About one-fifth of patients with ventricular aneurysm die suddenly, although rupture of aneurysm is rare.
10. For diagnosis, the EKG is helpful only about half the time.
11. Patients with severe congestive heart failure, refractory angina, recurrent ventricular tachyarrhythmias, and recurrent systemic emboli should be investigated for myocardial wall motion abnormalities and considered for surgical resection, revascularization, or both.
12. Surgery may increase the five-year survival rate to as much as 75%.

To study further the entity of ventricular aneurysm, and, more importantly, to help those afflicted with it, we need first to adhere to the strict Edwards' criteria when reporting data. Those patients at high risk for developing aneurysms, i.e., those with very high CPK rises, with hypertension, with valvular disease, and with persistent S-T segment elevation post-infarction, as well as those patients with S-T elevation on post-infarction exercise testing[60] should be followed prospectively with intracardiac blood pool scintiphotographs. If a ventricular aneurysm is suspected, the patient deserves strong consideration for surgery.

Acknowledgement

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A Disease Not to be Missed

Donald E. Ware, M.D., F.A.C.P.

Polymyalgia rheumatica and temporal arteritis are two clinical syndromes which are often associated and may be different expressions of the same process. These syndromes are of unknown etiology.

Polymyalgia rheumatica is a well-defined disease occurring in older people, more frequently in women than in men. It consists of pain and stiffness in the proximal muscles, primarily the neck, shoulders, and back, and sometimes the pelvic girdle. There is no stiffness of the joints. Morning stiffness may be marked, and there is often fever and malaise. The muscles involved are not tender, and there is a distinct lack of physical findings. The laboratory, however, is very helpful. Sedimentation rate is always very elevated, often over 100 millimeters/hour. Muscle enzymes and rheumatoid factors are normal.

Temporal arteritis also affects older people. Many patients have symptoms similar to polymyalgia rheumatica initially. They then develop severe headaches, which characterize this disorder. Unlike polymyalgia rheumatica, temporal arteritis has a distinctive histiologic lesion. In this syndrome there is a systemic inflammation affecting the medium to large size arteries. The inflammation classically affects the arteries of the head with giant cell granulomatous formation, fragmentation of the elastic fibers, intimal thickening, and thrombosis formation. Panarteritis is often present asymptomatically in people with polymyalgia rheumatica.

Polymyalgia rheumatica can cause pain and suffering and chronic disability. Temporal arteritis, however, has a most severe complication. By affecting the ophthalmic artery (and occasionally the occipital artery) the arteries can cause the abrupt onset of blindness. This may be unilateral or bilateral. Also, patients with temporal arteritis are at increased risk for developing other vascular problems, such as coronary occlusion or brainstem infarction.

The purpose of this article is to heighten the awareness of this disorder among physicians. It is a syndrome not to be missed. Its signs and symptoms can be dramatically eliminated by therapy. The terrible complications usually can be avoided with prompt recognition of the disease and appropriate treatment. Corticosteroids cause a dramatic and usually complete response. This response is seen within one or two days.

The incidence of temporal arteritis seems to be rising. The absolute incidence of temporal arteritis in the population is unknown. Hauser, et al[1] stated that the average annual incident rate was 2.9 per 100,000 for the entire population of Rochester, Minnesota. Houston, et al,[2] also from the Mayo Clinic, reported an overall annual incidence of 2.4 per 100,000 for the entire population of Olmstead County, Minnesota. The incidence in the population greater than fifty years of age was 17.4 per 100,000 for the years 1972-1974.

In Oxford County, with a population of less than 50,000, it would be expected that we would see one case or less per year. At Stephens Memorial Hospital over the last three years, from 1974 to 1977, there have been four cases recognized. Perhaps the increased incidence is due to the older population in this area of the state.

Three short case histories are presented to illustrate the signs and symptoms of this disease.

Case Histories

The first patient is an eighty-three-year-old female with complaints of visual problems for eighteen hours. This developed the day prior to her seeking medical attention. She noticed blurred vision but was not concerned and went to bed. The next morning when she awoke her vision was not improved. She noticed that the vision was only bad in her left eye and that she could see out of part of her left eye but not all of it. Because of that, she sought medical attention. On direct questioning the patient admitted to temporal skin pain but no headache. She denied fever or chills or muscle aches. On physical examination, the patient had erythema over the temporal areas and some tenderness over the temporal arteries. Their course was tortuous, and they were hard. Examination of the retina showed swelling of the optic nerve with a cotton wool spot inferiorly to the disc but without evidence of central retinal artery or branch artery occlusion. Her sed rate was 124. The patient was placed in the hospital and started immediately on intravenous steroids. She was given Solu-Medrol® 100 mg. intravenously and underwent a temporal artery biopsy, which showed giant cell arteritis. Patient was then placed on Prednisone 20 mg. p.o. q.i.d. The patient's vision continued to diminish. Prednisone was increased to 30 mg. p.o. q.i.d. Her vision in the other eye started to deteriorate. Prednisone was increased to 30 mg. every four hours and then to 40 mg. every four hours. Her vision continued to deteriorate slowly in both eyes to the point where she was completely blind. At the point that this happened, she was on 240 mg. of Prednisone a day.

The patient developed some chest pain, was transferred to the Intensive Care Unit, was placed on Propranolol and Hydrochlorothiazide. Her enzymes did not change. It was felt that she had myocardial ischemia rather than infarction. The steroids were slowly tapered. She left the hospital completely blind.

The second patient is a seventy-two-year-old man who came to the Emergency Room with complaint of severe headaches for several days and double vision. He was seen by the Emergency Room physician, who was worried that he might have temporal arteritis. On examination he had large tortuous, tender, temporal arteries. Sed rate was 120. He was admitted to the hospital and started on steroid therapy. Temporal artery biopsy showed giant cell arteritis. Within twenty-four hours his headache disappeared. Within two days he had no diplopia. At no time during this illness did he have any diminution in his vision in either eye. He continues to do well with a normal sed rate, and his prednisone is now 5 mg. per day.

The third case is a seventy-three-year-old female who came to the office complaining of headache for ten days. These were mainly localized to the temporal area. She had had some decrease in her vision for the past six months. She had noticed no change over the last few weeks. The patient also complained of a lot of lameness. She had pains in her hips and knees and a great deal of morning stiffness. She had trouble getting out of bed in the morning with

Continued on Page 431

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Statistical significance		$p<0.02$	$p<0.01$	$p<0.05$	$p<0.02$	$p<0.002$

*0 = No relief 1 = Partial relief 2 = Complete relief

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Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

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*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

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Comparative Study of Staple Vs Suture Anastomosis in Low Anterior Resection

RATNAKAR R. ANDALKAR, M.D., FACS*

After several years, surgical auto-suture stapling techniques are finally becoming popular in this country. In recent years, they are enjoying widespread acceptance. Many surgical residencies include a special rotation in order to learn stapling techniques. The first stapling device was developed almost 43 years ago by DePetz in 1927.[1] It remained stagnant until the mid-1960's when in Moscow, after several years of further research by the Research Institute of Experimental Surgical Apparatus and Instruments, a stapling device was developed which was quite practical but somewhat cumbersome. Gritsman described his techniques used in over 4,000 operations.[2] There followed more interest in the technique in this country and Ravitch published his results.[3] He has described in detail enteroanastomosis, closure of the duodenal, gastric, and intestinal stumps with wire staples and his techniques are being followed as a standard throughout this country and abroad. Gradually interest in stapling devices has been spreading outside the United States and there have been several articles from Great Britain describing experience with these devices, all articles having been quite favorable. A most recent article by Chassin compared suture technique against staple technique by the same surgeons and found no difference in postoperative complications after either technique.[4] Most recently another stapling device has been introduced, this called the EEA device, for end-to-end anastomosis. My surgical associate and I have started using this device as of one year ago after having been employing suture technique. This article compares our experience with this instrument as well as with another stapling instrument against results from prior suture technique. The staple technique has been used here since July 1978. A total of 13 patients had low anterior resection since that date and 10 of these were done with the EEA instrument and 3 with other stapling devices.

MATERIALS AND METHODS

Charts of patients seen by me in the last five years at Stephens Memorial Hospital, patients who had rectosigmoid malignancy and sigmoid diverticulitis were reviewed for complications. These complications are summarized in Table 1.

The only patient to develop anastomotic leakage also developed a wound infection. Many of the complications were considered relative. Complications such as myocardial infarction and pulmonary embolism are not included in the Table. In the suture technique used, one patient was included who had a para-sacral resection of the rectum for malignancy. The seventh complication not listed in this table was anal incontinence. None of the patients with staple technique had anal incontinence, whereas one patient, the one who had the para-sacral resection for malignancy, did have some incontinence to liquid stool. It is of interest to note that anastomotic obstruction is not seen in our experience with either technique whereas the literature claims this complication following the staple technique.

The youngest patient to have stapling was 21 years old, the oldest 81, and the mean age 67 years. The youngest patient for suture technique was 42 years, the oldest 82 and the mean 64 years. Table 2 summarizes this data.

TABLE 1

TABLE OF COMPLICATIONS COMPARING STAPLE VS SUTURE TECHNIQUE

Complications	*Staple Technique*	*Suture Technique*
1. Entero-cutaneous Fistula	0	0
2. Anastomotic Leak	0	1
3. Anastomotic Hemorrhage	0	0
4. Anastomotic Obstruction	0	0
5. Abscess around Anastomosis	0	0
6. Wound Infection	0	1

TABLE 2

TABLE OF COMPARING AGE OF PATIENTS IN STAPLE VS SUTURE TECHNIQUE

	Staple	*Suture*
Youngest	21 yrs.	42 yrs.
Oldest	81 yrs.	82 yrs.
Mean Age	67 yrs.	64 yrs.

TABLE 3

TABLE OF THE LEVEL OF ANASTOMOSIS COMPARED

	Staple	*Suture*
Least	5 c.m.	5 c.m.
Most	25 c.m.	25 c.m.
Mean	19 c.m.	14.6 c.m.

*Chief of Surgery, Stephens Memorial Hospital, Norway, Maine 04268.

Table 4

Table of Time Required for Operation in Staple VS Suture Technique

	Staple	*Suture*
Least	45 min.	150 min.
Most	255 min.	270 min.
Mean	145 min.	210 min.

Table 5

Table of Postoperative Hospitalization in Staple VS Suture Technique

	Staple	*Suture*
Least	5 days	6 days
Most	24 days	26 days
Mean	9 days	12.2 days

Table 6

Table Showing Malignant and Infectious Cases Compared Before and Since July 1978

	Prior to July 1978 Cases	*— Percentage*	*Since July 1978 Cases*	*— Percentage*
Malignancy	6	60%	9	69%
Infectious	4	40%	4	31%

Table 7

Table Showing Abdomino-Perineal Resection VS Low Anterior Resection Before and Since July 1978

	Prior to July 1978 Cases	*— Percentage*	*Since July 1978 Cases*	*— Percentage*
Abdomino-perineal resection	6	50%	3	23%
Low Anterior Resection	6	50%	10	77%

The level of anastomosis in each group is compared in Table 3. There were two patients who had an anastomosis at 5 centimeters from the anus with staple technique whereas one patient had an anastomosis at 5 centimeters using the suture technique.

The time required for each operation in the two categories is compared in Table 4. However, one case which took 45 minutes with stapling was a 21-year-old patient, extremely thin, and with a large fecalith with secondary inflammation around the sigmoid colon and secondary mucosal ulcerations. She had a staple anastomosis done but not with the EEA instrument.

The postoperative length of stay is compared in Table 5. The patient who stayed for 24 days was an 80-year-old woman who had a massive ventral hernia and was extremely obese. She had had repair of the ventral hernia as well as low anterior resection of the rectosigmoid and on the tenth postoperative day developed a massive pulmonary embolism which was successfully treated. The patient in the suture technique category who stayed for 26 days postoperatively had had an anastomotic leak with wound infection, healed after a diverting proximal colostomy.

Table 6 compares the differences in percentage of malignancy as compared to infectious cases in our two groups. Table 7 compares the total number of abdomino-perineal resections during the period for suture versus stapling technique.

No patient with either technique complained of diarrhea or bleeding from the anastomosis. The anastomoses which were palpable by finger on rectal examination postoperatively was felt to be adequate with either technique. Operative and postoperative mortality in both techniques was nil.

Technique

A standard technique was used in all patients. All had a colonic preparation without oral antibiotics but did receive two doses of prophylactic antibiotics prior to the surgery and were continued postoperatively on these antibiotics for at least three days. With the patient in a modified lithotomy position, under general anesthesia and with a foley catheter, the entire abdomen, perineum and genitalia were prepped and draped. After the usual approach into the abdomen and resection of the required length of colon, the edges to be anastomosed were prepared and purse strings applied on each end. The assistant surgeon then introduced the EEA instrument through the anus and opened it. Both ends of the colon to be anastomosed are brought to each cup of the instrument and their purse strings tied around each cup. The cups of the instrument are approximated and the instrument is fired. After the instrument is opened again by three full turns, it is removed by wiggling movements. Sigmoidoscopy is then performed by the assistant surgeon and the anastomosis inspected to check for any bleeding.

Discussion

This very small series of cases lacks any long-term follow up on patients who had stapling for anastomosis. Since the instrument has been used here only in the last year, we can draw no statistically significant conclusions but we did indeed find no major complications nor any contraindications for our continuing to use the stapling equipment for anastomosis instead of suturing. As can be seen in Table 4, the stapling was quite time saving. In addition, one could do low anterior resections more often with staple techniques and avoid abdomino-perineal resection as was seen in Table 7. With the use of the stapling, anastomosis as low as five centimeters from the anus could be done and the lumen felt quite adequate on finger palpation. The radiograph (Figure 1) shows the appearance of an anastomosis with staples, but this patient had not been using the anastomotic area

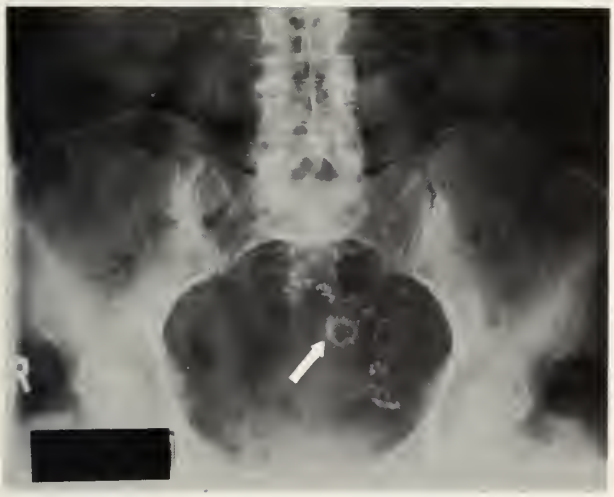


Fig. 1. Anastomotic staple ring in defunctional colon.



Fig. 2. Anastomotic staple ring on same patient in functional colon.

when that x-ray was taken, since she had had a proximal colostomy. After the colostomy was closed and the anastomotic area became functional, a subsequent x-ray (Figure 2) showed that the anastomotic area had become quite flexible and could be dilated at demand. As shown in this second radiograph, the anastomotic ring was quite wider than in the first radiograph. In this case, at least the argument that stricture develops with the use of stapling does not have much validity. In my experience, low anastomosis at 5 centimeters could not be done with sutures and in the conventional approach so that a parasacral approach had to be used. As shown in Table 5 stapling shortened the postoperative length of stay.

Every surgeon should, I feel, learn the staple technique which has been proven to be so beneficial to the patient.

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A Disease Not To Be Missed—*Continued from Page 428*

lots of aches and pains in her muscles. As the day progressed the pain would get better. The patient stated that rather abruptly her headaches started to occur, and these were mainly in front of her ears. They would radiate up into her temples. She had seen a local physician who had given her aspirin with codeine, which seemed to help.

Examination showed tender temporal arteries. Ophthalmologic examination was normal. Laboratory revealed a sed rate of 115. Temporal artery biopsy showed giant cell arteritis. She was started on high dose steroids, and her headache disappeared almost immediately. Her myalgias also rapidly regressed. She was discharged to home on 40 mg. of Prednisone each day.

The patient continues to do well with a sed rate of 30 on 10 mg. of Prednisone twice a day.

The presentation of this syndrome may be variable, but the diagnosis must be considered in any older patient (almost always over fifty) with visual complaints or headaches, especially in the temporal area. Even with a normal examination of the temporal arteries, a sed rate should be obtained. If the sed rate is markedly elevated, a temporal artery biopsy should be done. The diagnosis is an easy one to make and the disease easy to treat if it is only considered. If it is missed, the results are catastrophic. It is a disease not to be missed.

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Asymptomatic Urine Infections in Children

William T. Whitney, Jr., M.D. and Carleton A. Plaisted, R.N.*

Introduction

Urinary tract infection is a common pediatric problem, and a sizeable literature on childhood urinary tract infection has developed recently. There is the widespread assumption that untreated urinary tract infection can occasionally lead to structural renal damage and renal failure. Also, recent studies indicate that asymptomatic bacteriuria (ABU) occurs more frequently than does infection associated with symptoms. Large populations of children—mostly girls—have been studied. With remarkable uniformity a prevalence of ABU has been established of between 1 and 2% of girls.[1,2,3] Between 0.4 and 0.6% of girls originally uninfected become bacteriuric with each year of follow-up. Five percent of girls will have had at least one urinary infection by the end of high school.[1,4]

Girls with ABU who have had radiologic evaluation are often found to have an abnormal intravenous pyelogram (IVP) or voiding cystourethrogram (VCUG). Between 13 and 20 percent show renal scarring and/or loss of renal parenchymal mass; between 21 and 30 percent have vesico-ureteral reflux.[2,3,5] The radiographic changes of pyelonephritis, if present, are usually manifest at the time of the first identified urinary infection. We are therefore advised to obtain an IVP and VCUG soon after the discovery of the first urinary infection in all children.[6]

We are also urged to screen all girls for ABU because of its high incidence and because of possible structural renal damage associated with untreated infection. Urine culture represents the best method for diagnosing infection, and screening urine cultures are therefore recommended as part of health supervision in children. The recommendation is found in the H.E.W. *Guide to EPSDT Screening*[7], in a review article on screening in pediatric practice,[8] in a recent edition of a pediatric textbook,[9] and in a recent statement from the Section on Urology, American Academy of Pediatrics (which recommends screening only in pre-school age girls).[10]

Questions arise, however. If 5% of all girls will have had one urine infection by the end of high school, and if all girls with their first infection are to have an IVP and VCUG, as recommended, then a remarkable increase will occur in costs, workload for radiology departments, and in radiation exposure. The British authors of studies of screening for ABU do not favor universal screening.[11,12] A critical analysis of a screening program needs to examine the costs and effort involved, the frequency in the population of the condition screened for, and whether or not there exists an effective treatment.

Our study tries to answer the following questions; 1) What is the best method of screening for ABU?, and 2) Does identification and treatment of ABU make a difference in regard to the health of the child? Our conclusions are based on experience during eight years of pediatric practice and on a review of the literature on urinary tract infection in children.

Methods

Our experience with urinary infections in children is divided into two parts. First, we retrospectively reviewed the charts of children with urinary infections seen between 1970 and 1974. Some of these children had had their first infection prior to 1970. We then prospectively undertook to screen for urinary tract infection in children presenting to our practice between Sept. 1977 and May 1979. The setting for the earlier phase was a four-man pediatric department within a multi-specialty group in a semi-rural area of New Hampshire; the latter part of the study comes from a two-person pediatric practice in rural Maine. In both situations, urine cultures were obtained from all girls during health supervision visits. We screened only girls because of the markedly increased frequency of urinary infections in girls compared to boys. Screening cultures were obtained only in girls old enough to void voluntarily and who were under age 17. Urine cultures were also obtained in any child at any visit when clinically indicated. Clinical data prompting us to obtain a urine culture included a history of previous infection, dysuria, eneuresis, frequency, hesitency, urgency, vomiting, diarrhea, vaginal itching, unusual smell of the urine, abdominal pain, flank pain, and fever. We also obtained a culture as part of the evaluation of perineal rash, small stature, abdominal tenderness, and chronic constipation.

A file on children with urine infections was maintained by a nurse who was responsible for patient education and for recalling children for periodic follow-up urine cultures after they had had their first infection. The diagnosis of urine tract infection was based on either 1) a combination of a culture showing a single organism with a colony count greater than 10^5, bacteriuria evident on microscopy, and appropriate signs and symptoms, or 2) at least two urine cultures with a single organism and a significant colony count with organisms seen microscopically, for girls who were asymptomatic. The specimens were obtained midstream after Zephiran® washing of the external genitalia and drying with a sterile pad. Infants were cultured using "U-Bags." Suspicious or positive results were followed by a repeat specimen. Urethral catheterization with a # 5 Fr. feeding tube was used in infants to obtain

Continued on Page 434

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†See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
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Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: Autonomic neuropathy. Hepatic or renal disease. Ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension. Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include: xerostomia; urinary hesitancy and retention; blurred vision and tachycardia; palpitations; mydriasis; cycloplegia; increased ocular tension; loss of taste; headache; nervousness, drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs.

Usual Dosage: Bentyl 10 mg. capsule and syrup: *Adults*: 1 or 2 capsules or teaspoonfuls syrup three or four times daily. *Children*: 1 capsule or teaspoonful syrup three or four times daily. *Infants*: ½ teaspoontul syrup three or four times daily. (May be diluted with equal volume of water.) Bentyl 20 mg.: *Adults*: 1 tablet three or four times daily. Bentyl Injection: *Adults*: 2 ml. (20 mg.) every four to six hours intramuscularly only. NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE: The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing. CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

Product Information as of October, 1978

Injectable dosage forms manufactured by CONNAUGHT LABORATORIES, INC., Swiftwater, Pennsylvania 18370 or TAYLOR PHARMACAL COMPANY, Decatur, Illinois 62525 for MERRELL-NATIONAL LABORATORIES, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215, U.S.A.

Merrell

MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc.
Cincinnati, Ohio 45215, U.S.A.

either the initial specimen or to confirm any persisting positive specimens using the bags. The cultures were incubated at once and the results were read at 24 and 48 hours.

In the first two years of the study "Testuria"® was used for culturing; since 1973 we have used "Culturia"®, a dip slide with a different media on each side. Many, but not all, positive cultures were confirmed by using full culture technique using a hospital laboratory. After the first urinary infection, children were recalled for follow-up cultures every three months for the first eighteen months, thereafter every 6 or 12 months. They also had a culture done 2 to 4 days after the initiation of therapy and another done 10 to 14 days after the completion of treatment. IVP's and VCUG's were obtained in the following situations: all males with a first infection, all girls with a first infection who were under age two and who had upper tract signs and symptoms, and in other girls after their second or third infection. Children were referred to a urologist if they had an obstructive lesion, reflux, hydronephrosis, or other major anomaly, and also when they had five or six infections.

Results

Between 1970 and 1974 we identified 240 children, age three months to sixteen years, who had at least one urinary infection. Ninety-four girls of this group had at least two infections. The sex ratio was 231 to 9, female to male. On chart review, we could find no symptoms or previous illness prior to the time of the first infection that would have predicted the infection in fourteen of the 240 (5.8%). These presumably represent "asymptomatic" bacteriuria. One hundred and sixty-two of the 240 (67.5%) were followed by cultures for more than one year: 35 for less than two, 52 for two to three years, 37 for three to four years, and 38 for more than four years. Twenty-two of these 162 girls (13.6%) had at least one asymptomatic infection.

Ninety-two children—boys and girls—had both an IVP and a VCUG. Thirty-four of the group had an abnormal radiograph, of which 24 (26%) could be classified as a major anomaly. One boy had a unilateral non-functioning kidney, and another had posterior urethral valves, bilateral hydroureter, and hydronephrosis. One girl who presented with renal failure and infection at three months had bilateral dysplastic kidneys. Three children had renal scarring on IVP, one associated with reflux. One girl had bilateral vesico-ureteral reflux of moderate severity repaired surgically before 1970. The remaining seventeen girls mostly had minor degrees of reflux, with a few showing bladder diverticula. The minor abnormalities in the remaining ten children included: double collecting systems, caliectasis, bladder trabeculation, and increased post voiding bladder volume. Forty-eight of the 94 girls with two or more infections saw a urologist. Apart from the girl noted above with repaired reflux, no child had a surgical procedure other than cystoscopy and/or urethral

dilation.

We also examined the effect of the duration of therapy for the initial infection on the likelihood of recurrence. Of 137 children treated between 1970 and 1974 for at least six weeks initially, 41 (29.9%) had no recurrence. Of the 78 children treated for four or less weeks for the initial infection, 33 (42.3%) had no recurrent infection during the period of our follow-up.

The second part of our study, the surveillance of urinary infections occurring between Sept. 1977 and May 30, 1979, demonstrated the following results. Three hundred and fifty-three girls presented themselves for health supervision care and were able to provide a specimen for culture. Three hundred and sixty-two negative cultures were obtained from this group; no positive culture was found. One hundred and seventy-nine girls presenting themselves to our office for either a health supervision visit or for care for an illness had clinical indications prompting us to obtain a urine culture. One hundred and fifty-two of these girls had 160 negative cultures; 27 of them had at least one urinary tract infection. Only one of the 27 had her urinary infection discovered at a health supervision visit, and she was hardly asymptomatic—a ten-year-old girl with Turner's Syndrome and a past history of urinary infection.

Thirteen of the 27 girls have had both an IVP and a VCUG; eight were normal, five abnormal. A sixteen-year-old girl had unilateral reflux and hydronephrosis. The other four had more minor anomalies including a unilateral double collecting system, mild unilateral renal scarring (present on an IVP done five years previously), urethral dilitation and bladder diverticula, and grade I unilateral reflux.

Discussion

Proponents of universal screening of girls for ABU point out its ease of implementation, its low cost, and its reliability. Using the methods for screening urine cultures results in neither an increase of false-positives, nor false-negatives.[13] Specimens for urine culture are quite easy to obtain in an office setting, and the cost is modest—75 cents for a single unit of "Culturia." Recent studies indicate that when samples are inoculated promptly, neither the external genitalia need to be cleaned, not the specimen collected in a sterile cup.[14]

The earlier portion of our study indicates that 5.8% of urinary infections presented without symptoms. Would these children have remained undiscovered without screening? The quality of the history is difficult to assess from a retrospective review of office charts with several physicians recording data. Possibly a few of the allegedly asymptomatic girls had symptoms or past history suggestive of urinary infection not recorded in the chart. Moreover, between 66 and 76% of the girls with ABU in the three large surveys had symptoms or history suggesting the possibility of infection. These girls then were not truly asymptomatic, and could have been discovered by a complete history. The populations of these studies—Dundee, Newcastle, and Albemarle County, Va.—included many children of lower socioeconomic class. These children may have lacked access to care, and many may not have had the benefit of adequate history taking. If some of these children had sought care earlier for their urinary tract symptoms, they might have been removed from the ranks of ABU, or possibly would not have had a positive culture at time of screening. Perhaps ABU would be less prevalent in surveys of girls with easy access to care, unimpeded by economic or educational factors. A study of bacteriuria in 5,379 girls seen by the Kaiser-Permanente system for multi-phasic screening indicated a prevalence of only 0.5%, as did a survey of 3,270 girls from a practice in Virginia.[15]

Our failure to discover one girl with ABU from the 353 presenting for well child care without urinary symptoms supports the notion that truly asymptomatic bacteriuria is unusual indeed. We suggest that it will remain uncommon if the medical history is complete. From the first portion of our study we noted that 13.6% of the 162 girls with at least one infection followed for one year or more had at least one asymptomatic infection. These cultures were obtained at the time of routine post-infection follow-up, and questions were asked by the nurse to exclude urinary symptoms occurring during the interval period. Asymptomatic infection seems to occur in these children with a frequency sufficient to justify post-infection screening. This is especially true if not all children are to be studied radiographically after their first infection.

What would be the hazard of not discovering the few girls who are truly non-symptomatic with their infection? Possibly treatment would make little difference in either the persistence of the infection or the rate of recurrence. One study followed the course of 110 schoolgirls found on screening to have bacteriuria and noted that the 59 who received no antibiotic therapy had no more persistence or recurrence of infection during the following year than did the 51 who were treated.[16] Kunin states that the older the girl and the more time allowed to elapse between the first infection and subsequent ones, the less likely will be the bacteriuria to recur; these effects were independent of treatment. He also observed that eighty percent of the time reinfection occurred with a different species or serotype of *E. coli* than those causing the earlier infection. The girl with ten or more infections was no less likely to eventually remit than the girl with only one infection. In his study, two-thirds of the girls with reinfections had symptoms at the time of recurrence.[17] There seem to be biologic differences between the strains of *E. coli* causing asymptomatic infections from those causing infections with symptoms. Those causing the former are more likely to show spontaneous agglutination and are more likely to be sensitive to the bactericidal effect of normal serum than are strains causing symptomatic infections. The author speculates that they may have an altered cell wall and be less virulent than strains causing infections with symptoms.[18] We conclude that the

failure to discover ABU would probably not be harmful to the child in regard to persistence or recurrence of infection.

Does undiagnosed urinary infection lead to progressive renal damage as measured by radiographic findings? Also, are children with abnormal x-rays more likely to have infection than children with normal studies? Renal scarring or loss of renal parenchymal mass does not seem to progress after its initial discovery, especially if reflux is not present.[19] There was no increase in major radiographic abnormality with increasing age of the girl at the time of the initial discovery of bacteriuria.[20] The existence of x-ray abnormalities does not seem to predispose girls to infection; recurrence of infection for Kunin was no more likely in girls with reflux than in those without.

The presence of abnormalities on IVP or VCUG in our experience did not seem to necessitate surgical therapy, especially in girls whose infections were diagnosed after 1970. The meatotomies and urethral dilitations that were performed may have been unnecessary.[21] Also surgery is unlikely to be recommended based on the presence of reflux alone. In more than eighty percent of cases reflux disappears after five years.[22] Whether children with isolated reflux, without renal scars, should receive chronic antibiotic prophylaxis or not is controversial. Therefore, failure to identify ABU probably would not deprive the child of beneficial medical or surgical therapy.

The few children with renal scarring or loss of renal mass deserve further consideration. Their number is small—0.05% in the Newcastle study; but they are at potential risk of developing renal failure. These changes of pyelonephritis can progress if they coexist with reflux. If children with this combination of problems could be identified, they could be offered chronic antibiotic therapy and close bacteriologic and radiographic monitoring, care that might reduce future morbidity. Smellie, however, found that most often these severe structural changes were present at the time the child was first studied, often in early infancy.[23]

Perhaps then screening for bacteriuria should be directed to the preschool aged girl. One study of preschoolers gives a prevalence of 0.9%; the other 3.6%. The former study examined children aged three to five; the latter only girls under two. Six of the infected children in the study of infants showed reflux of which three progressed to mild renal scarring on follow-up IVP.[24,25] Also in this report the data were derived from a practice setting, and the authors made use of a "urinary diary." Mothers recorded the presence of frequent diaper changing, weak urinary stream, and dribbling in their babies. Of particular interest is that the urinary diary identified 23 of the 25 infants with urinary infection.

The incidence of pyelonephritis and reflux in girls with ABU may not be as great as the surveys cited above indicate. Another study shows only ten percent with pyelonephritis and only 20 percent with reflux.[26] Our experience is also consistent with a diminished frequency. Only 26 percent of our 92 children who had an IVP and VCUG had significant abnormality, and in most of them only minor degrees of reflux were present. Because we did not perform studies on girls over age two with their first infection, there remains the possibility that the girls without x-rays performed had significant abnormalities. The question of the frequency of radiographic abnormality in girls with urinary infection seen in primary care practice deserves, we believe, further scrutiny.

Attention has recently been devoted to the relationship of the level of the infection in the urinary tract—upper or lower—to the presence or absence of structural change. Fever during a urinary infection apparently correlates well with the presence of renal parenchymal loss on IVP and with reflux.[27] If indeed structural change is more likely in children with infection of the upper tract, then methods useful in identifying upper tract infection might be helpful in selecting children who should receive radiologic evaluation. Methods for localization of the level of infection that are under study include antibody titers, C-reactive protein, and renal concentrating ability.

Conclusion

We have examined several problems relating to urinary tract infections in children with special attention to the question of screening for asymptomatic infection. Our conclusions are based both on our own experience and from a review of the literature.

1. The conscientious physician need not screen for urinary infection in asymptomatic girls. Asymptomatic infection may be rare; a complete history will serve to identify most children with urinary infection. The consequences of failing to recognize asymptomatic infection seem insignificant. Screening should probably be directed toward infants and younger pre-schoolers, a population at much more risk from undiagnosed infection than older girls are.

2. Continued study needs to be devoted to methods for screening of infants with urinary infection, methods for identifying infections of the upper tract, and criteria for identifying children with urinary infection who may not need radiographic study.

3. A urine culture should be obtained in any child whose clinical evaluation raises the slightest possibility of urinary infection.

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Serum Creatine Phosphokinase Isoenzyme (MB Form) in Myopathy Due to Electrolyte Depletion*

Case Report

JOHN G. MEHARG, JR., M.D.**

ABSTRACT

Proximal myopathy developed in a patient with multiple severe electrolyte abnormalities secondary to malabsorption due to regional enteritis. Elevated muscle enzymes were noted, including the presence of CPK-MB, without good evidence for myocardial infarction. All findings were corrected by repletion of electrolytes and treatment of the inflammatory bowel disease.

Increased serum creatine phosphokinase (CPK) activity is indicative of disease or damage of a number of body tissues,[1] usually skeletal muscle,[2] since this tissue has by far the largest amount of CPK.[3] When isoenzyme analysis has been performed, and the MB isoenzyme found to be present, then cardiac muscle has been stated to be the source of the elevation,[4] since no other tissue has significant amounts of this isoenzyme.[3] Thus, presence of CPK-MB in the serum has been proposed as a specific marker for myocardial infarction (MI).[5,6,7]

However, other etiologies for the presence of CPK-MB have been reported, including polymyositis,[8] dermatomyositis,[8] various muscular dystrophies,[9] viral myositis,[8] ischemic rhabdomyolysis,[10] and heat stroke.[11] In most of these cases diffuse striated muscle disease was present, and it is possible that the MB fraction came from cardiac muscle as part of a generalized muscle disorder. I report here a case in which high levels of serum CPK with presence of MB isoenzyme were found as a result of severe electrolyte depletion with myopathy.

CASE REPORT

A 57-year-old woman was referred for evaluation of progressive weakness and fatigue of four months' duration. She also complained of crampy lower abdominal pain, relieved by vomiting or passage of foamy, foul-smelling diarrhea, and a 12 pound weight loss. To some extent she had had these latter symptoms intermittently since 1962, when an evaluation for fever resulted in exploratory laparotomy with partial small bowel resection, and a diagnosis of regional enteritis was made. She had been on no special diet or medication since that time. She denied any other symptoms suggestive of primary cardiovascular, endocrine, or neuro-muscular disease.

Examination revealed a pale tremulous white female, appearing older than her stated age, with a temperature of 100.2 degrees F. and a resting pulse of 104 beats per minute. Blood pressure and respirations were normal, and her weight was 98 pounds. Her tongue was red, smooth and shiny. No thyroid enlargement or bruit was noted. There was no muscle tenderness, but there was mild proximal muscle weakness, more marked in the lower extremities. The abdomen was slightly distended but soft and nontender with active bowel sounds and no masses or organomegaly. The remainder of the physical examination was within normal limits.

Pertinent laboratory abnormalities included the following: Hematocrit 30% with normochromic normocytic RBC indices; Albumin 3.3 gms.%; Calcium 4.8 mg.%; Phosphorus 2.3 mg.%; Magnesium 0.6 mEq/L; Potassium 2.1 mEq/L; Aldolase 4.6 units (normal 0.5-3.1); and CPK 5330 IU/L with MB fraction reported present. Stool fat stain was positive, with an abnormally high 72-hour stool fat excretion, and the D-xylose test was also abnormal. Thyroid studies were normal. Radiographs of the small bowel were interpreted as compatible with sprue. EKG showed sinus tachycardia with T wave inversions in leads II, III, aVf, and V3-6.

The patient was felt to have severe malabsorption on the basis of inflammatory bowel disease, and was treated with electrolyte repletion, hematinics, prednisone, and salicylazosulfapyradine. On this regimen her strength improved, her diarrhea disappeared, and her laboratory and EKG abnormalities rapidly reverted to normal. At no time in her clinical course did she have any history or physical findings to suggest myocardial infarction, and serial EKG's were not consistent with evolution of MI.

DISCUSSION

That electrolyte disorders of this degree can cause muscle weakness is well documented,[12,13,14,15] and that electrolyte depletion of this degree with resultant muscle damage can result from regional enteritis alone has been reported.[16] Myoglobinemia and myoglobinuria were used as indicators of muscle damage, but more recently elevation of serum enzymes, including aldolase and CPK, have been utilized as indicators.[2] However, in none of the prior reports was CPK isoenzyme analysis performed. In the other muscle disorders in which CPK-MB has been noted, it could be postulated that the isoenzyme "leaked" from cardiac muscle as a result of the heart's being involved by a systemic disorder. In the case reported here a similar mechanism has been postulated in view of the known effect of these electrolyte disorders on the integrity and/or function of striated muscle.

Several criticisms can be made of my hypothesis. The first is that good documentation against the diagnosis of MI is lacking. LDH isoenzyme analysis and vectorcardiography would have been helpful. However, the EKG changes noted were short-lived, coincident only with the electrolyte changes in the patient's clinical status, and quickly

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reverted to normal with electrolyte repletion. Furthermore, it is known that electrolyte changes of the degree found in this case can produce EKG changes such as the ones noted here.[17,18,19] Finally, the patient's clinical picture in no way suggested acute MI.

Second, it may be argued that the extremely high total CPK volume may have flooded the test system, producing a wide diffuse band on electrophoresis, with extension into the region of migration of the MB fraction, producing a false-positive. This seems unlikely since other reports using similar techniques, of CPK elevation even higher than the total reported here, did not report any such overlap problem.[20] Also, it is our laboratory's policy to report only a separate band as positive.

Third, there is no biopsy-proven myopathy. However, the clinical findings of proximal muscle weakness which improved with treatment would certainly argue in favor of a myopathy, especially when the initial abnormalities were at a level previously shown capable of producing myopathic changes.[12,13,14,15]

In conclusion, I feel that the evidence presented supports a diagnosis of proximal myopathy, and does not warrant a diagnosis of MI. Since the presence of the MB fraction has been said to be virtually specific for myocardial infarction,[5] it would seem important to document those conditions which can produce an elevation of serum CPK with MB fraction without the presence of MI. Several such conditions have already been so documented. I now suggest addition of electrolyte depletion with myopathy to that list, and urge caution in the use of CPK-MB as the only marker of MI.

Summary

A case of proximal myopathy secondary to depletion of the potassium, magnesium, phosphorus, and/or calcium is reported. Elevation of serum CPK with presence of MB isoenzymes without MI is noted.

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Infected Epidural Hematoma Simulating Traumatic Leptomeningeal Cyst

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While a leptomeningeal cyst is a relatively rare post-traumatic lesion, its roentgen diagnosis in the child following skull fracture is usually not difficult and the plain film findings in the proper clinical setting are characteristic and have been considered virtually diagnostic[2,5,12,13,15] (Fig. #1a and b).

Our experience with a child developing a post fracture epidural empyema or abscess is reported below because the roentgen findings simulate those usually associated with the more familiar post-traumatic arachnoidal cyst.

CASE REPORT

This fourteen-year-old mentally retarded, epileptic, negro male was seen in the Emergency Service of Germantown Hospital, Philadelphia, Pennsylvania, on December 7, 1967, because of a laceration of the scalp in the left frontal area resulting from a blow on the head by a metal pipe. The laceration was closed with two chromic, four black silk, and three dermalon sutures. Examination was otherwise negative. There had been no loss of consciousness and the patient was sent home after tetanus toxoid administration to be followed in the Surgical Outpatient Clinic. Slight headache persisted for one day and a twelve hour episode of status epilepticus, the first for ten years, came five days later. The sutures were removed after ten days but the wound never healed. There was recurrent bleeding and a discharge and swelling were noticed. Examination on January 19, 1968 revealed a granulomatous lesion in the forehead and a defect could be palpated by hemostat in the frontal bone. Topical Neosporin® ointment and oral Penicillin G 600,000 units Q.I.D. were prescribed and roentgenograms of the skull were obtained (Fig. #2). A mildly depressed left frontal skull fracture was demonstrated in the area of the injury where now a protruding and pulsating soft tissue mass was visible and palpable. The diagnosis of leptomeningeal cyst seemed likely and the child was admitted to the hospital for surgical exploration. There was no fever but some drowsiness was noted by this time. White blood cell count was 3,900 per mm^3, hemoglobin 13 Gm%. On January 26, 1968, a transcoronal left frontal craniotomy was performed under endotracheal general anesthesia. An empyema was found in a thick, organized, epidural hematoma and removed surgically along with an adherent dura. Temporalis fascia was used to replace the excised dura. The skin and tissue removed showed acute and chronic nonspecific inflammation and foreign body type granulomatous reaction histologically and cultures obtained at surgery showed no growth. The child made a good recovery and was discharged ambulatory and afebrile on the twelfth postoperative day. Re-admission was necessary on March 9, 1968 to adjust the dosage of anti-convulsant medication because of drowsiness resulting from over-sedation. At this second admission, lumbar puncture revealed an opening pressure of 70 mm. of C.S.F. The C.S.F. was clear, colorless, and contained 28 mg% protein, 104 mg% sugar, 90 lymphocytes per mm^3, and showed no growth on culture. Carotid angiography was normal. Skull x-ray showed a left frontal surgical bone flap and chest x-ray was normal. The white blood cell count was 4,200 mm^3, hemoglobin 15.8 Gm%, urinalysis normal, B.U.N. 6 mg%, fasting blood sugar 100 mg%, CO_2 25 mEq.%.



Fig. 1A. Right lateral radiograph of the skull demonstrating a wide and long comminuted fracture in the right parietal bone of four-year-old boy.



Figure 1B. Same projection as in Fig. 1A four months later. The fracture line has enlarged to a longitudinal cleft with smooth, scalloped margins. Other areas of the fracture demonstrate healing. Typical location and appearance of leptomeningeal cyst.

DISCUSSION

The primary care physician, neurosurgeon, and radiologist who deal with cranial trauma in children are ever alert to the uncommon but potentially serious complication of skull fracture that may occur when there is a large rent or tear in the dura mater.[15] These fluid-filled arachnoidal herniations through the dural tear prevent dural healing and enlarge progressively to erode the adjacent bone and compress

*Director of Radiology, Stephens Memorial Hospital, Norway, Maine 04268.

**Director of Radiology, Germantown Dispensary and Hospital, Philadelphia, Pennsylvania 19144.



Figure 2: Left lateral radiograph demonstrating fracture in left frontal bone of 14-year-old boy six weeks after blunt trauma. Note the wide cleft with smooth, scalloped margins and the absence of bone reaction. This erosion of the fracture margins by an infected epidural hematoma cannot be differentiated from that demonstrated in figure 1B due to leptomeningeal cyst.

the underlying brain.[8,10,11,14] They are most often seen in the long, linear, and widely separated fracture, particularly in the posterior parietal area and usually in children. It is common practice, therefore, to follow the healing of all such fractures in children by re-x-ray to be sure the fracture line is not enlarging with the development of a leptomeningeal cyst.[3]

In the case presented here, the findings seemed typical for traumatic leptomeningeal cyst and commitment to this diagnosis was heightened by experience with such a case proven shortly before (Fig. #1). The treatment, fortunately, was not compromised by the misdiagnosis since both lesions are treated by similar surgical approach and a good result was obtained in both cases. The feature of the epidural empyema that was atypical for leptomeningeal cyst was the frontal rather than posterior parietal bone location. Also, the age of the patient was more typical for epidural hematoma.

Epidural hemorrhage occurs in 1 to 3.1% of cranio-cerebral injuries.[4,6,7] Gurdjian and Webster reported seven in a series of 647 skull fracture patients.[7] They may result from rupture of the middle meningeal arteries and veins, dural sinuses, or diploic and emissary vessels. Middle meningeal hemorrhage is the most common.[16] They are almost always unilateral and the classic clinical presentation of a lucid interval followed by unconsciousness with focal signs is well known. As the hematoma strips dura away, tearing the connecting veins between the diplöe and the dural surface, further bleeding occurs and the lesion may enlarge rapidly.[9] Occasionally such a clot may occur without fracture. They are less common in infancy, more frequent after the age of ten, but most typical in young adult life. The dura mater is more adherent to the bone in infancy. The Surgeon General of the United States Army reported

Continued on Page 441

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Brief Summary

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Nausea and vomiting of pregnancy.

PRECAUTIONS
Because of potential drowsiness, Bendectin should be prescribed with caution for patients who must drive automobiles or operate machinery.
Studies in rats and rabbits have revealed no suggestion of drug-induced fetal abnormalities at doses of Bendectin up to 90 times the maximum human dose. In addition, several epidemiologic studies in women who received Bendectin during pregnancy have shown that the incidence of birth defects in their offspring is no higher than in women not taking the drug during pregnancy. Nevertheless, like all drugs considered for use during pregnancy, particularly during the first trimester, Bendectin should be used only when clearly needed.

ADVERSE REACTIONS
The adverse reactions that may occur are those of the individual ingredients. Doxylamine succinate may cause drowsiness, vertigo, nervousness, epigastric pain, headache, palpitation, diarrhea, disorientation, or irritability.
Pyridoxine hydrochloride is a vitamin that is generally recognized as having no adverse effects.

DOSAGE AND ADMINISTRATION
2 Bendectin tablets at bedtime. In severe cases or when nausea occurs during the day: 1 additional Bendectin tablet in the morning and another in midafternoon.

Product Information as of January, 1978

References:
1. Meyer, C.: American Folk Medicine. Scarborough, New York, Plum Books — New American Library, 1975, p. 208.
2. Data on file, MERRELL-NATIONAL LABORATORIES Division of Richardson-Merrell Inc. Cincinnati, Ohio 45215

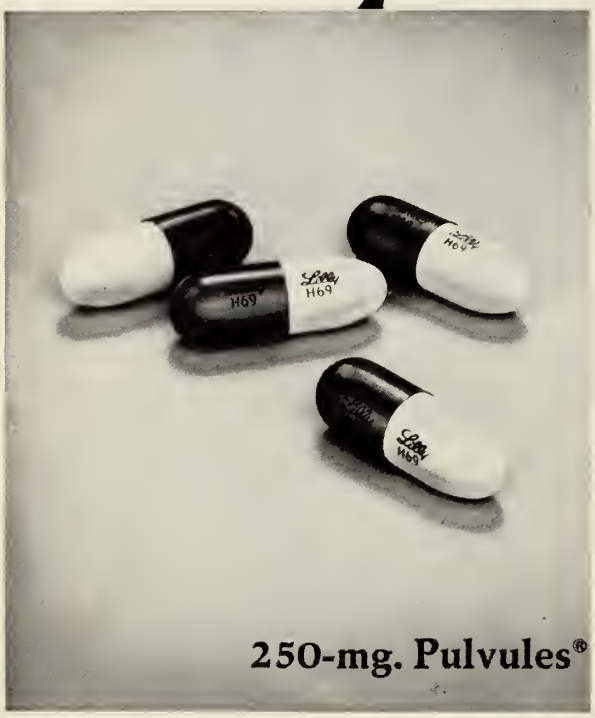
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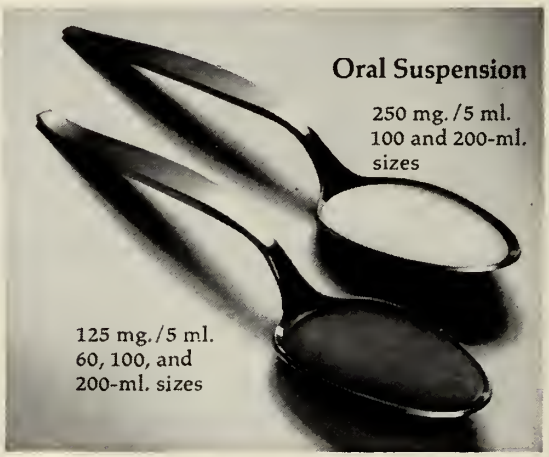
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extra dural hematoma in 20% of Korean War compound skull fracture patients.[1]

Epidural abscess is more common in the vicinity of the middle ear and the frontal sinuses but as in our patient may be a sequel to either unrecognized or imperfectly treated compound fracture of any part of the cranial vault.[2] If no osteomyelitis develops and no intra-dural extension occurs, it is very difficult to diagnose with certainty. Low grade fever, drowsiness, headache, localized edema of the scalp, stiffness of the neck, increased cell count or protein in the cerebrospinal fluid without microorganisms in a patient who previously seemed to be recovering from the immediate effects of head injury are the findings that should arouse suspicion of such a lesion. There may be focal signs and focal seizures. These findings plus an x-ray showing a fracture implicating the middle ear or frontal sinuses strengthens the diagnosis. There is a wide variation in the clinical picture. As with epidural hemorrhage, epidural abscess may occur without skull fracture. There may be no lucid interval before the onset of confusion or unconsciousness or as in our patient, there may be no period of loss of consciousness.

Computed tomography is the non-invasive diagnostic procedure of choice in the diagnosis of intracranial hemorrhage, but this method of diagnostic imaging had not yet been introduced at the time this case was evaluated.

Conclusions

The possibility of an epidural empyema or infected epidural hemorrhage must be considered in the differential diagnosis of the child with an enlarging skull fracture. As exemplified by the case presented, this entity can very closely simulate the clinical and roentgen complex considered characteristic for a traumatic leptomeningeal cyst.

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From the Secretary's Notebook

Summary of 1979 Annual Meeting of the M.M.A. House of Delegates June 16 and 17, 1979 at Rockport, Maine

The 126th Annual Session of the M.M.A. House of Delegates was held at the Samoset Resort Inn in Rockport, Maine with a registered attendance of eighty delegates and alternates and twenty-five guests. The first session was convened on Saturday, June 16 at 2:00 P.M., and the second session on Sunday, June 17 at 2:00 P.M. Francis I. Kittredge, M.D., President of the M.M.A. called to order the meetings of the House, which were presided over by George W. Bostwick, M.D., Speaker of the House.

Election of Speaker and Vice-Speaker of the House of Delegates for 1979-1980 — George W. Bostwick, M.D., was re-elected Speaker, and A. Dewey Richards, M.D., was re-elected Vice-Speaker.

Budget for 1980 — The Budget, as presented by Dr. Richard Leck, was approved, with expenditures for 1980 estimated to be $301,636.00. Further recommendations were also *approved* as follows:

a) That $60,000 be withdrawn from the MIT Fund,
b) That each active member of the M.M.A. be assessed $40 to be paid by September 1, 1979,
c) That M.M.A. dues be increased by $100 in 1980, and
d) That dues increases be determined by using the all items Consumer Price Index, starting in 1981.

It was further recommended by the Reference Committee that, in the future, the Association adopt and adhere to a balanced budget.

Committee on Nominations — A slate was prepared in April at the Interim Meeting of the House of Delegates and presented at this meeting for vote. Nominated from the floor were Drs. Donald Robertson (6th District) and Craig Young (9th District). The following officers were elected:

President-Elect
Robert E. McAfee, M.D., Portland
AMA Delegate
Robert E. McAfee, M.D.
AMA Alternate Delegate
Brinton T. Darlington, M.D., Augusta
Executive Committee
1st District—Robert F. Ficker, M.D., Kennebunkport
5th District—Paul A. Brinkman, M.D., Farmington
6th District—Donald M. Robertson, M.D., Harrington
9th District—Craig W. Young, M.D., Presque Isle (to complete Dr. Helfrich's unexpired term)

The **Standing Committees**, constituted per recommendation of the Committee on Nominations, were *approved* with the following additions: Dr. David Eitel to the Committee on Allied Health Professions, Dr. Peter Leadley to the Committee on Continuing Education, and Dr. Craig Young to the Committee on Government Health Activities.

Reports not included in the House of Delegates' folders—

Report of Legislative Committee — Dr. John Dow, Chairman of the Committee reported on its activities during the past year.

AMA Delegate — Dr. Robert McAfee reported on activities of the AMA and spoke at considerable length about increasing membership.

Cost Containment — Dr. Thomas Ballantine, Jr., of Boston, a member of the AMA Board of Trustees, spoke and gave a slide presentation on Cost Containment.

Cumberland County Second Opinion on Elective Surgery Program — Dr. Clement A. Hiebert reported on the results of the program which is just completing its first year.

Medical Mutual Insurance Company of Maine — Dr. William Maxwell reported on the current status of the Company.

Printed Reports not requiring action (resolutions from committees appear elsewhere in this summary) and accepted for information were as follows: **Committees**—Allied Health Professions, Recruitment, Aid & Placement, Health Care Financing, Peer Review, Maine Committee—AMA-ERF, Conservation of Vision, Diabetes, Joint Practice, Maternal & Child Welfare, Amy W. Pinkham Fund, School Health, and Burn Advisory; Reports of Secretary-Treasurer, Executive Committee Chairman and Members and Delegates to Out-of-State Medical

Society Meetings.

RESOLUTIONS

M.M.A. Headquarters—The original resolution presented by the Penobscot County Medical Society was defeated and the following substitute resolution presented by the Reference Committee, was *approved:*

WHEREAS: The Maine Medical Association has bought a headquarters building in Augusta, Maine; and

WHEREAS: The benefit derived from ownership and use of such facility will accrue to the membership during the next forty years; and

WHEREAS: The House of Delegates has voted a $100 assessment on each member, which could deter new members from joining, impose an undue hardship on present members, and be unjust to retiring members;

THEREFORE BE IT RESOLVED: That the $100 assessment be rescinded by the House of Delegates of the Maine Medical Association and the cost of the building be amortized by financing the said building over an appropriate period of years, thereby assessing the beneficial users of the building during its useful life.

Dues — Presented by the Executive Committee, this resolution was unanimously *approved:*

WHEREAS: The Maine Medical Association encourages active membership of all physicians practicing within the State of Maine; and

WHEREAS: Membership dues may represent a barrier to those physicians just commencing practice after residency;

THEREFORE BE IT RESOLVED: That active membership dues be halved for physicians applying for such membership during the first calendar year of practice after residency.

Note: The intention of this resolution would be to halve the half-year rate paid by those joining directly after completion in late June of a residency, or halving the full-year rate paid by those joining directly on completion of a residency in late December of 1979 or later.

Term of AMA Delegate and Alternate — Presented by the Executive Committee, this resolution was unanimously *approved:*

To Amend Chapter IV, Section 7 of the M.M.A. Bylaws, the third sentence from the end so as to read: "No member shall be eligible for more than three consecutive terms in any of the above-mentioned offices, except for the offices of Delegate and Alternate-Delegate to the American Medical Association."

Representation on the Executive Committee — Presented by the Executive Committee, the resolution was amended and *approved:*

WHEREAS: The present bylaws of the Maine Medical Association provide for representation on the Executive Committee by representatives of nine districts; and

WHEREAS: Only five counties have individual representation on the Executive Committee; and

WHEREAS: The other districts represent two or three counties, many of which feel that the present representation on the Executive Committee has served to effectively disenfranchise them; and

WHEREAS: The original representation according to district was based on the historical development of the medical association and recognized the reality of great distance and sparse populations in the various counties of the State of Maine;

THEREFORE, BE IT RESOLVED: That the Maine Medical Association recommends that each county medical society be represented by one member on the Executive Committee of the M.M.A.;

That such representative be recommended to the Nominating Committee by the county medical societies for election at the House of Delegates meeting in November 1979;

That such representatives serve staggered terms consistent with the bylaws until elections at the annual meeting of the House of Delegates;

That such representatives will assume office on January 1, 1980.

Monitoring Votes — This resolution, submitted by the Androscoggin County Medical Society and asking that the M.M.A. act during future legislative sessions to instruct the lobbyists for the M.M.A. to carefully monitor the votes of each legislator on health-related issues, was *defeated.*

M.M.A. Health Insurance Plan — This resolution, presented by the Androscoggin County Medical Society and amended by the Reference Committee, was *approved* as follows:

WHEREAS: It is desirable for the Maine Medical Association to have the best group health insurance program possible at the reasonable price;

BE IT RESOLVED: By the Maine Medical Association that it seek competitive bids for group health insurance for its members, their families, and their employees, at their earliest practical time, to include health insurance with a deductible clause or provision.

High Blood Pressure — Presented by the Executive Committee, this resolution was *approved:*

WHEREAS: High blood pressure is a major factor in the pathogenesis of heart attack, heart failure, kidney failure and stroke; and

WHEREAS: A multitude of unco-ordinated programs for screening of hypertension in the State of Maine have been developed; and

WHEREAS: The Maine High Blood Pressure Council has been formed to set standards for the detection, referral, follow-up and treatment of hypertension in order to reduce confusion and duplication of efforts; now

THEREFORE, BE IT RESOLVED: That the Maine Medical Association endorses the Maine High Blood Pressure Council as representing the best interests of both Maine patients and their physicians; and

BE IT FURTHER RESOLVED: That the Maine Medical Association supports the efforts of the Maine High Blood Pressure Council to develop quality standards for the detection, referral, follow-up and treatment of hypertension in the State of Maine.

National Health Care — The original resolution was presented by the York County Medical Society, and defeated. The following substitute resolution was presented by the Reference Committee and *approved:*

WHEREAS: The topic of National Health Insurance is a key concern of the 96th Congress; and

WHEREAS: The purported purpose of such legislation is to improve the quality and to lower the cost of medical care; and

WHEREAS: During the 13 years in which the Department of Health, Education and Welfare has had the opportunity to perfect the programs now in force, its inefficiency has yielded only accelerated inflation and policies which promote inflation; and

WHEREAS: The U.S. Government in its network of V.A. and military hospitals has the opportunity to lead the way in cost containment, bed utilization and end results of care, but has published no statistics on these areas;

THEREFORE, BE IT RESOLVED: That the Maine Medical Association advise our Congressional delegation to postpone any extension of National Health Programs until the Department proves its ability to upgrade the administration of existing programs and its ability to operate Government hospitals in a fashion superior to that existing in civilian hospitals. It is further suggested that identical accounting and quality review methods be used in comparing the two systems.

Reports of Reference Committees — Recommendation (not listed elsewhere in this summary) is as follows:

Committee on Continuing Education — The Reference Committee recommended that the Resolution within the report not be acted upon at this time.

Maine Blue Cross and Blue Shield Award of Appreciation — This year's award was presented to Dr. Bradley E. Brownlow of Blue Hill.

Out-of-State Delegates — The following delegates spoke briefly of the major problems in their respective states and extended greetings on behalf of their societies: Dr. George Way, New York; Dr. John Sherwin, New Hampshire; Dr. Raymond James, Connecticut; and Dr. Robert Conrad, Rhode Island.

Special Memberships — The recommendations by the county societies for special memberships were *approved.*

Health Care Financing — Dr. Harry Bliss, Chairman of the M.M.A.'s Committee on Health Care Financing, gave a status report of discussions that have evolved between Blue Shield and the Committee on HCF subcommittee over the past 15 months. The subcommittee asked for the House's approval in concept of the results of these discussions with Blue Shield, as well as continuing further negotiations along the same lines. It was *approved.*

Tribute to Dr. Hanley — All fifteen county medical societies participated in a farewell tribute to Dr. Hanley who is retiring as Executive Director after 24 years.

Stenographic Record — A summary of the proceedings of the House of Delegates is to be sent to members of the House of Delegates. It will also be published in a forthcoming issue of the *Journal of the Maine Medical Association.* The complete transcript is on file at the Association's office in Augusta, where it is available for examination by any member of the Association.

The meeting was recessed at 4:54 P.M. on Saturday, June 16, and was adjourned at 5:15 P.M. on Sunday, June 17.

PATRICIA A. BERGERON
Secretary-Treasurer, M.M.A.

Annual Meeting Dates For Your 1980 Calendar...

Maine Medical Association, June 12-15

The Balsams, Dixville Notch, New Hampshire

BOARD OF REGISTRATION'S PROPOSED CME REQUIREMENTS WILL BE SUBJECT OF PUBLIC HEARING - - -

The Board of Registration in Medicine will hold a public hearing on November 28 concerning the new Continuing Medical Education requirements enacted by the 109th Legislature. Information on the time and place of this public hearing will be published in major newspapers on November 7 and 21. The Board's proposed Continuing Medical Education requirements will be 20 hours of Category I credit and 30 hours of Category II (includes categories II through V of MMA classification) credit each calendar year. Effective in 1982 the cost of relicensure will be raised from $25 to $50.

SHORT STRAWS - - -

The National Health Planning and Resources Development Act of 1974 (PL 93-641) was passed on January 14, 1975. Implementation of this law calls for the creation of HEALTH SYSTEM AGENCIES to regulate and oversee health plans at the federal, state and local levels. In our neighboring State of Rhode Island a waiver was granted and the planning process will be done by existing state agencies acting with the STATE HEALTH COORDINATING COUNSEL (SHCC). This combination will in effect be the Health Systems Agency. The ultimate power for health plans will reside with the Rhode Island Department of Health.

The Rhode Island Society of Anesthesiologists, composed of 55 clinicians, demonstrated an interest in a thick tome entitled "Preliminary Draft, State Health System Plan of the Rhode Island Department of Health". One reason for this interest is found in the section headed *SALARY HOSPITAL-BASED SPECIALTY SUPPORT PHYSICIANS / Tactical Recommendation / By 1983 ALL HOSPITAL-BASED SPECIALTY SUPPORT PHYSICIANS SHOULD BE COMPENSATED BY SALARY. Associated Strategies (1) Encouragement of Efficient Hospital Use from the Institutional Perspective: a) by 1983 there should be published annual reports of average total cost per patient day and patient day adjusted for age and case mix by hospital. Included in these reports should be comparable data on the costs of treating diagnostically related groups of patients at each hospital. b) By 1983 there should be established for hospitals minimum size standards which take into account economies of scale and institutional service capabilities." (2) Specialty Support Physician Intervention Recommendation: "In 1983 the total numbers of patient care anesthesiologists, pathologists and radiologists should be 50, 37, and 63, respectively."*

Lest there be any question about the intent, in a later section is a paragraph entitled *Short Range Intervention Recommendation. In 1983 THE TOTAL NUMBERS OF ACTIVE IN PATIENT CARE ANESTHESIOLOGISTS, PATHOLOGISTS AND RADIOLOGISTS IN RHODE ISLAND SHOULD BE LIMITED TO 50, 37, and 63, RESPECTIVELY.*

The short range intervention recommendation to have 50 anesthesiologists, 37 pathologists, and 63 radiologists in 1983 is based on decreasing by one quarter the differential between the 1975 Rhode Island ratios as indicated by the SEARCH (R.I. HEALTH SERVICES RESEARCH, INC.) data and their HMO counterparts.

Alternative Rejected "Laissez-faire" policy - rejected as inefficient. Continuation of the present fee for service polocies is likely to result

ontinued high volume and, perhaps, unnecessary utilization of hospital-ased specialty support physician services. Although data do not exist or calculating the cost of continuing the "laissez-faire" policy in hode Island, a rough calculation of the national cost of fee for service eimbursement policies in 1975 was made by the Health Research Group ounded by Ralph Nader.

ell-informed sources in Rhode Island say that it appears that Certif-cate of Need legislation already enacted for capital and program ex-ansion may also be considered for residents in training and MD's wish-ng to practice in the State.

ut back to the Anesthesiologists -- anyone wish to draw straws?

NDROSCOGGIN COUNTY MEDICAL ASSOCIATION OPENS NEW OFFICE - - -

he Androscoggin County Medical Association has opened a new office at 1 Campus Avenue in Lewiston. By calling the Association at its new elephone (783-7017), members of the public may seek advice or ask ques-ions about medical practice in the communities of Lewiston and Auburn nd surrounding towns.

n influx of young doctors into Lewiston-Auburn over the past few years as prompted the Association to assume a higher profile according to a pokesman for the group. The spokesman indicated that while the county ssociation planned to be more vocal on matters of community awareness f health care issues, it will speak out on issues which affect the med-cal profession as a whole and not on individual local issues which ight become divisive.

hen asked if the Medical Association would take a stand on the expan-ion programs planned by two local hospitals, Dr. Edward Z. Walworth, ecretary of the Association replied, "There's been very little discus-ion of that."

EPARTMENT OF DEFENSE SEEKS CIVILIAN PHYSICIANS - - -

he United States Military Enlistment Processing Command (MEPCOM) is urrently recruiting civilian physicians to conduct pre-enlistment physical examinations at various Armed Forces Examining and Entrance Stations throughout the United States. Starting salary is currently $30,017. A vacancy exists in Portland and further information may be secured from Mr. Dan Rosin, MEPCPO,Ft. Sheridan, Illinois 60037.

NESTHESIOLOGIST RVG CASE MAY BE APPEALED - - -

The American Society of Anesthesiologists' legal counsel has been notified that the Department of Justice has filed a protective notice of appeal in the Relative Value Guide case recently decided in the Society's favor. This notice is designed to preserve the Government's right of appeal pending a final decision as to whether to proceed with an appeal.

The potential for litigation seems endless.



CONTINUING MEDICAL EDUCATION IN MAINE

Conferences and Workshops

Title: **Symposium on Family Dynamics**
Date: December 1, 1979
Location: Sheraton Inn, S. Portland (Exit 7—round tower at Maine Mall)
Sponsor: State of Maine Academy of Family Physicians
Credit: AAFP (prescribed)—4 hours
Symposium followed by Annual Business Meeting, Maine Chapter of American Academy of Family Physicians. For further information contact Roger E. Condit, M.D., Farmington, Maine; 778-6521.

Hospital Activities

Augusta General Hospital
Augusta, Maine

Nov. 27, 1979: **Obstetrics**
7:30-9:30 a.m. Visiting Professor from Dartmouth
This program has been certified AMA Category I and AAFP (prescribed). For further information contact Mrs. Nancy York; 623-4711. This program may be viewed over ITS.

Augusta Mental Health Institute
Augusta, Maine

Nov. 29, 1979	**Liability in the Clinical Setting**	10-11:30 a.m.
	Practical Legal Aspects of Mental Health Care Delivery	1:30-3 p.m.
	James Vaccarino, J.D., Director of Legal Affairs, Massachusetts General Hospital	
Dec. 6, 1979	**Current Programs in Alternative Living**	10-11:30 a.m
	Alternative Living Unit	
Dec. 13, 1979	**Recent Findings in the Chronic Use of Hallucinogens**	10-11:30 a.m.
	The Nature of Knowledge in Psychiatry	1:30-3 p.m.
	Henry Abraham, M.D., Clinical Instructor in Psychiatry, Harvard Medical School; Clinical Associate in Psychiatry, Massachusetts General Hospital	

The 10-11:30 a.m. Sessions are Grand Rounds; 1:30-3 p.m. Sessions are Inpatient Psychiatry Courses. All programs have been certified AMA Category I. For further information contact Pauline H. Soper; 622-3751.

Eastern Maine Medical Center
Bangor, Maine

Every Mon.	EEG Conference	12-1 p.m.
Every Mon.	Surgical Service—Chief's Rounds	5-6 p.m.
4th Mon.	ENT Section Meeting	12-1 p.m.
4th Mon.	Neurosurgery Section Meetings	4-5 p.m.
3rd Tues.	Dermatology-Pathology Conference	5-6 p.m.
3rd Tues.	Dermatology Section Meeting	6-7 p.m.
4th Tues.	Pulmonary Medicine Section Meeting	8-9 a.m.
1st Wed.	Hematology/Oncology Meeting	8-9 a.m.
Every Wed.	Tumor Clinic Conference	2-5 p.m.
Every Wed.	Radiology Conference (1) Ultrasound/Nuclear Medicine (2) Radiology Film Review (3) Neuroradiology (4) Teaching File Conference	5-6 p.m.
1st Thurs.	Ophthalmology Section Meeting	7:30-8:30 a.m.
	OB-GYN Conference (1) Pathology (2) GYN Analysis (3) OB-Pediatric Combined (4) In-Service and Education	8-9 a.m.
Every Thurs.	Pediatric Grand Rounds	9-10 a.m.
Every Thurs.	Medical Service Conference	10-11 a.m.
Every Thurs.	Cardiology Conference	11 a.m.-1 p.m.
2nd Thurs.	Orthopedic Grand Rounds	7:45-8:45 a.m.
4th Thurs.	Orthopedic Service Meeting	7:30-9 a.m.
4th Thurs.	Surgical Service Death Review	7:45-8:45 a.m.
Every Thurs.	Psychiatric Service Grand Rounds	10-11 a.m.
4th Thurs.	Urology Section Conference	7:30-8:30 a.m.
Every Fri.	Neurology Grand Rounds	8-9 a.m.

Visiting Professor Program:

2nd Thurs.	Medical Service Visiting Professor	10 a.m.-5 p.m.
2nd Thurs.	Anesthesia Service Visiting Professor	7-8 a.m.
3rd Thurs.	OB/GYN Service Visiting Professor	10 a.m.-4 p.m.
Saturdays	Surgery Service Visiting Professor	8 a.m.-Noon
4th Thurs.	Pediatric Service Visiting Professor	10 a.m.-5 p.m.
as scheduled	Orthopedic Service Visiting Professor	
as scheduled	Family Practice Visiting Professor	
as scheduled	Psychiatric Service Visiting Professor	
as scheduled	Radiology Service Visiting Professor	

All activities have been certified AMA Category I. For further information contact Robert H. Brown, M.D., Chairman, Med. Ed. Committee; 947-3711 Ext. 330.

Henrietta D. Goodall Hospital
Sanford, Maine

Nov. 20, 1979	**"Advances in the Treatment of Diabetes Mellitus"** Louis Bignati, M.D., Joslin Clinic, Harvard Medical School, Boston, Massachusetts	
Dec. 20, 1979	**"Office ENT"** Arnold Katz, M.D., New England Medical Center, Tufts University School of Medicine, Boston, Massachusetts	

The meetings will be held at the Henrietta D. Goodall Hospital's Conference Room at 7 p.m. These programs have been certified AMA Category I. For further information contact Melvin Bacon, M.D.: 324-3632.

Maine Medical Center
Portland, Maine

Every Mon.	Student Technologist Conference	8 a.m.
Every Mon.	Hematology Pathology Conference	11 a.m.
Every Mon.	Pulmonary Conference	12 Noon
Every Mon.	Pediatric Residents Conference	1 p.m.
Every Mon.	Anesthesia Formal Resident Lecture	3:30 p.m.
Every Mon.	Surgical Pathology Review	4 p.m.
Every Mon.	Radiology Journal Club	5 p.m.
1st & 3rd Mon.	Clinical Nephrology Conference	11 a.m.
1st & 3rd Mon.	Hematology-Pathology Conference	12 Noon
3rd Mon.	Eye Conference	11:45 a.m.
Every Tues.	Radiology Residents' Seminar	7 a.m.
Every Tues.	Family Practice Grand Rounds	9 a.m.
Every Tues.	Electrocardiographic Interpretation	1 p.m.
Every Tues.	Psychiatric Grand Rounds	1:30 p.m.
Every Tues.	Anesthesia Formal Resident Lecture	3:30 p.m.
Every Tues.	Surgical Seminar	4 p.m.
Every Tues.	Pathology Slide Seminar	4 p.m.
1st & 3rd Tues.	Radiology Pathology Conference	12 Noon
1st & 4th Tues.	Neurology Conference	12 Noon
2nd Tues.	Infectious Disease Conference	12 Noon
3rd Tues.	Hematology Conference	12 Noon
5th Tues.	Oncology Conference	12 Noon
Every Wed.	Radiation Therapy Conference	7 a.m.
Every Wed.	Urology Conference	7 a.m.
Every Wed.	Student Technologist Conference	8 a.m.
Every Wed.	Continuing Education Seminar	8 a.m.
Every Wed.	Medical Conference	9 a.m.
Every Wed.	Psychiatric Journal Club	12 Noon
Every Wed.	Cardiology Seminar	12 Noon
Every Wed.	Surgical Grand Rounds	5 p.m.
2nd Wed.	Guest Internist—Medical Conference	9 a.m.
4th Wed.	Medical Mortality Conference	9 a.m.
Alt. Wed.	Neurology-Psychiatry Seminar	11 a.m.
Alt. Wed.	Anesthesiology Journal Club	3 p.m.
Every Thurs.	Thoracic Surgery Conference	7 a.m.
Every Thurs.	OB/GYN Conference	7 a.m.
Every Thurs.	Anesthesiology Clinical Conference	7 a.m.
Every Thurs.	Diagnostic Radiology Teaching Conference	7 a.m.
Every Thurs.	Surgical Conference	8 a.m.
Every Thurs.	Pediatric Conference	9 a.m.
Every Thurs.	Tumor Consultation Board	11 a.m.
Every Thurs.	Medical Resident Conference	12 Noon
Every Thurs.	Surgical Seminar	4 p.m.
Every Thurs.	Endocrinology Conference	5 p.m.
Every Thurs.	Dental Specialty Lecture	6 p.m.
1st Thurs.	Anesthesia Mortality Conference	7 a.m.
1st Thurs.	Guest Pediatrician	9 a.m.
1st & 3rd Thurs.	Gastroenterology Conference	12 Noon
1st & 3rd Thurs.	Cardiac-Surgical Conference	12:30 p.m.
1st, 3rd, & 5th Thurs.	Pulmonary Physiology Conference	12:30 p.m.
2nd Thurs.	Cardiology Teaching Conference	12:30 p.m.

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2nd Thurs.	Eye Staff Scientific Session	5:30 p.m.
2nd Thurs.	Maine Medical Center Medical Staff Meeting and Scientific Session	6 p.m.
2nd & 4th Thurs.	Pulmonary-Pathology Conference	12 Noon
2nd & 4th Thurs.	Endocrinology Conference	12 Noon
3rd Thurs.	Combined Guest Physician or Guest Surgeon Program	8 a.m.
3rd Thurs.	Clinical Anesthesiology Lecture Series	3:30 p.m.
4th Thurs.	Surgical Mortality Conference	8 a.m.
4th Thurs.	Anesthesia Mortality Conference	3:30 p.m.
Last Thurs.	Pediatric Mortality Conference	9 a.m.
Every Fri.	Thoracic Surgical Conference	7 a.m.
Every Fri.	Nuclear Medicine Conference	7 a.m.
Every Fri.	Student Technologist Conference	8 a.m.
Every Fri.	Neurological Neurosurgical Conference	8:30 a.m.
Every Fri.	Gastroenterology Conference	9 a.m.
Every Fri.	Medical Rehabilitation Staff Conf.	9 a.m.
Every Fri.	Orthopedic Conference	9 a.m.
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3rd Fri.	Rheumatology Conference	12 Noon
4th Fri.	Oncology Conference	12 Noon
Alt. Fri.	Oncology Radiation Conference	7 a.m.
Alt. Fri.	Gastroenterology Conference	10 a.m.

All programs have been certified AMA Category I. For further information contact Costas T. Lambrew, M.D.; 871-2111

Mercy Hospital
Portland, Maine

Dec. 6, 1979, 7-8 p.m. — **Recent Advances in Proctology**
Winthrop S. MacLaughlin, M.D., Mercy Hospital, Portland, Maine

Dec. 11, 1979, 8-9 a.m. — **The Lung and Special Environments: Air, Sea & Space**
William A. Demicco, M.D., Mercy Hospital, Portland, Maine

These programs have been certified AMA Category I. For further information contact Harold Pariser, M.D.; 774-1461, Ext. 363

Mid-Maine Medical Center
Waterville, Maine

Nov. 29, 1979 — **Herpes Simplex Encephalitis**
Marvin Eisengart, M.D., MMMC
David Ginder, M.D., MMMC

Dec. 6, 1979 — **Genetics for the Clinician**
Paul LaMarche, M.D., EMMC

Dec. 13, 1979 — **Problems of Adolescence—Drugs**
Andrew Guthrie, M.D., Massachusetts General Hospital, Boston

Dec. 20, 1979 — Case Presentation—Family Practice Residents

All programs run from 12-1 p.m. and have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621. These programs may be viewed over ITS.

St. Mary's General Hospital/Central Maine Medical Center
Lewiston, Maine

Nov. 23, 1979, 8-10 a.m. — Joint Surgical Grand Rounds—St. Mary's General Hospital

Dec. 14, 1979, 8-10 a.m. — **Nutrition**
Robert McGandy, M.D.
Tufts University School of Medicine, Boston, Massachusetts

These programs have been certified AMA Category I. For further information, contact Mrs. Phyllis Dube; 786-2901, Ext. 230

V.A. Hospital
Togus, Maine

Dec. 5, 1979, 1:15-2:15 p.m. — **Medical Service Staff Meeting**
John Menges, M.D., V.A. Hospital

Dec. 12, 1979, 1:15-2:15 p.m. — Medical Service Staff Meeting—Review of Records

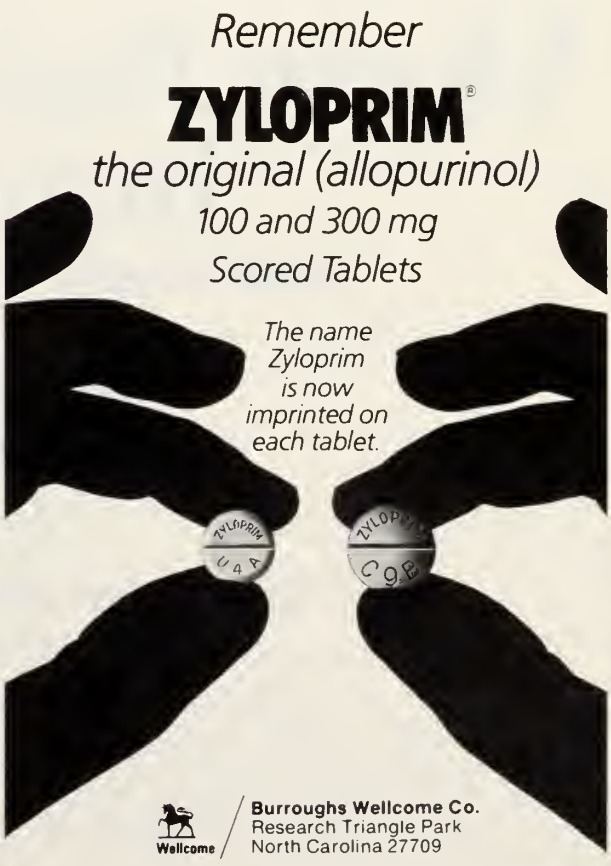
Dec. 19, 1979, 1:15-2:15 p.m. — **Medical Service Staff Meeting**
John Miller, M.D., V.A. Hospital

Programs have been certified AMA Category I. For further information contact E. Osborne Coates, Jr., M.D.; 623-8411.

The Webber Hospital
Biddeford, Maine

Dec. 4, 1979, 8-9 a.m. — **Chronic Obstructive Pulmonary Disease**
John Urbanetti, M.D., Tufts University School of Medicine, Boston, Massachusetts

This program has been certified AMA Category I. For further information contact Ms. Doris Smith; 282-5901, Ext. 227



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Penobscot Bay Medical Center Issue

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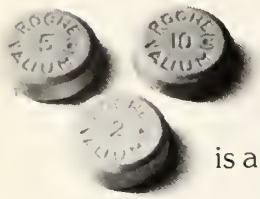
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Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

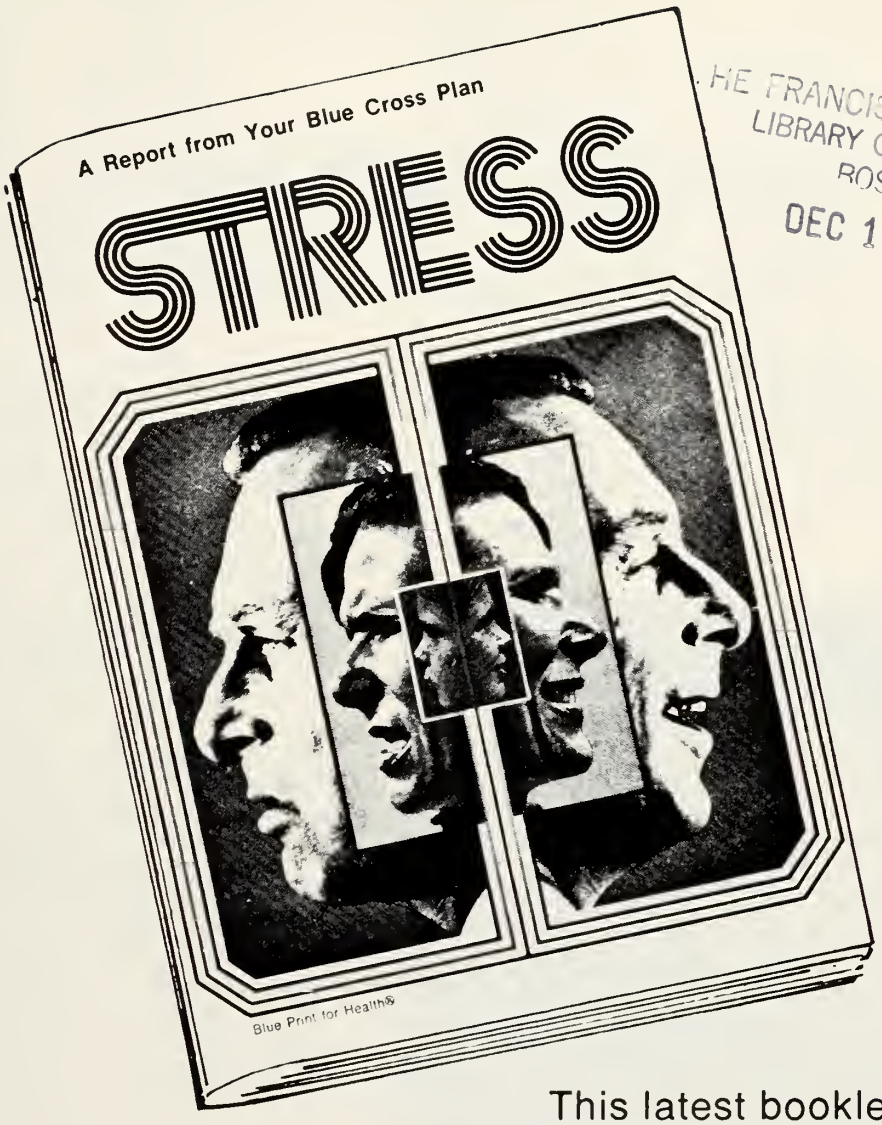
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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Maine Medical Association

Volume Seventy | Augusta, Maine, December 1979 | Number 12

Albert Ludwig Sigesmund Neisser: 1855-1916

Tribute to a Venerable Physician

Richard J. Kahn, M.D., F.A.C.P.*

To mark the 100th anniversary of the discovery of the etiologic agent causing gonorrhea, it seems fitting to take a brief look at the man whose name lives on attached to that villainous organism, *Neisseria gonorrheae.*

Gonorrhea was a disease well known prior to the epidemic of syphilis in 1493.[1] For the subsequent 250 years there was confusion and controversy about the causes of gonorrhea and syphilis. Many believed, as did Thomas Sydenham in the early 18th century, that they were different manifestations of the same disease. He wrote: "It is an hundred years ago since it (French Pox) shew'd itself first in the Species of a virulent Gonorrhea, and does so still, endeavoring to go off that way, and it has no other manifest Symptom, only in a very small Ulcer in the Privities, commonly call'd a Shanker, is the first sign of the Disease; the Venom whereof, because it cannot be carry'd off by a Gonorrhea, invades and infects the Blood presently."[2] Hermann Boerhaave, another superior clinician of the day, considered them to be two different diseases, which opinion went unheeded.

In 1786 John Hunter set out to prove them to be two manifestations of the same disease.[3] Some controversy exists over the details and significance of his self-experimentation. He introduced the urethral discharge of an executed criminal, alleged to have gonorrhea, into the glans of his penis with a lancet. Generalized syphilis developed over the following three years, convincing Hunter that the gonorrhea and syphilis were one disease. It would appear, from our present knowledge, either that the criminal had *both* gonorrhea *and* syphilis or that Hunter had another nonexperimental Luetic contact.

Philippe Ricord reintroduced the speculum uteri, and proved through extensive clinical, epidemiological, postmortem, and experimental studies that the two diseases were separate. Between 1831 to 1837, he inoculated the afflicted patients with secretions of their own disease. When pus from a chancre was inoculated elsewhere it produced a chancre, not gonorrhea; likewise when secretions of urethral discharge from gonorrhea were similarly tested,

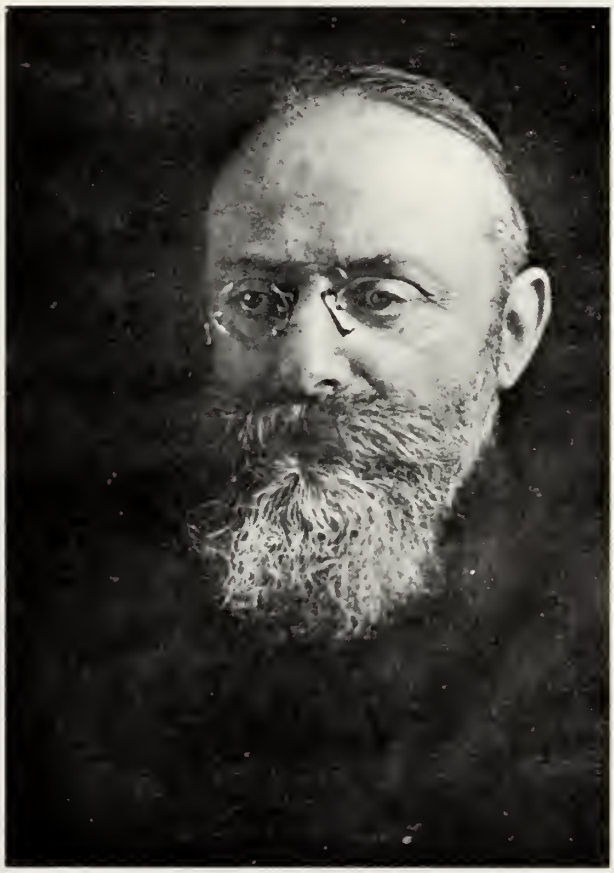


Fig. 1. Albert Ludwig Sigesmund Neisser: 1855-1916.

*Department of Medicine, Penobscot Bay Medical Center, Rockland, Maine 04841.

Continued on Page 453

Observations on the Daily Incidence of Acute Appendicitis in a Community Hospital

Lloyd Roberts, M.D.*

Acute appendicitis is not a very glamorous disease. No one has presented it as a model for unraveling the mysteries of molecular biology, nor does it provide fertile ground for the proliferation of medical technology. It is however still the most common reason for emergency surgery and as such deserves a little attention once in a while. Over the years, we have gotten the impression we were seeing more acute appendices early in the week than late in the week. The following study of admissions for acute appendicitis over a two and a half year period in an active community hospital is presented as confirmation of this impression.

Patients and Methods

Computer printout records from the Penobscot Bay Medical Center Medical Information Service were reviewed. These printouts break down all admissions into categories by discharge diagnosis. Since the discharge diagnosis of acute appendicitis is based on the Pathologic diagnosis and most of the diagnoses were made by the author, there seemed to be no need to review this material. Virtually all patients admitted with a diagnosis of acute appendicitis are operated on within a few hours or at the most 24 hours of the time of admission, so that the date of admission is used as the index date in this study.

Results

As can be seen in Figure 1, there is a clear daily difference in admission for acute appendicitis. The admissions peak on Sunday, Monday and Tuesday and fall to a low on Wednesday, Thursday, Friday and Saturday. The mean admissions per day of the peak days is 23.3 cases and the mean of the slow days is 16.5 cases for the two and a half years examined.

Discussion

The surgeons tell us that acute appendicitis has an incubation period of a few hours to a day or two judging from the history of abdominal pain. If this is so, there is clearly something about the weekend which increases susceptibility to or causes for acute appendicitis. The principle difference between the weekend and the weekdays is of course that the majority of us work during the week and do not work on weekends. It is tempting to suggest that the incidence of appendicitis and its associated strain on the national economy could be significantly reduced by instituting a seven day work week. This would have a double benefit of greatly increasing the productivity of the nation, probably solidifying the dollar and certainly maintaining our position in the world hierarchy.

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WED	XXXXXXXXXXXXXXXX
THU	XXXXXXXXXXXXX
FRI	XXXXXXXXXXXXXXXX
SAT	XXXXXXXXXXXXXXXXX
SUN	XXXXXXXXXXXXXXXXXXXXXX

Fig. 1. Daily distribution of admissions for acute appendicitis.

The principle feature of the weekend then is that it is a focal point of non work and therefore presumed recreation. Recreation in this country is usually characterized by excesses of one form or another. The principle excesses are, not necessarily in order of incidence or importance, television, exercise, exposure to the elements, eating, drinking, sleeping, and fornication. Exercise as a cause of appendicitis would simply not be accepted by health authorities who are firmly committed to the health-exercise ethic. Exposure to the elements seems an unlikely etiologic factor as appendicitis is a disease of modern man and exposure to the elements decreases proportionately with civilization. Sleeping can probably be discarded as more or less of a constant. This leaves, eating, drinking, and fornication to be considered. The latter two probably can be ruled out as a significant portion of patients with acute appendicitis are in the pediatric age group and hopefully are not sexually active or drinking. We are left then with dietary excess as the most likely weekend factor to be associated with appendicitis.

Dr. Burkitt,[1,2] proponent of the cellulose deficiency syndrome and its association with the Industrial Revolution, points out that acute appendicitis was a medical curiosity and rarity until the introduction of refined cellulose deficient food. Interestingly, he also notes that of the disease syndromes which he attributes to cellulose deficiency all have a time lag of years between the onset of civilization and the increased incidence of the disease in question with the exception of appendicitis. Populations who make an abrupt change in eating habits to Western refined cellulose deficient foods have an immediate and dramatic increase in the incidence of acute appendicitis.

We postulate that the high weekend incidence of acute appendicitis is related to the dietary excesses of the weekends. If this is so then Thanksgiving, which is certainly the annual national focal point for dietary excess, should be followed by an immediate increase

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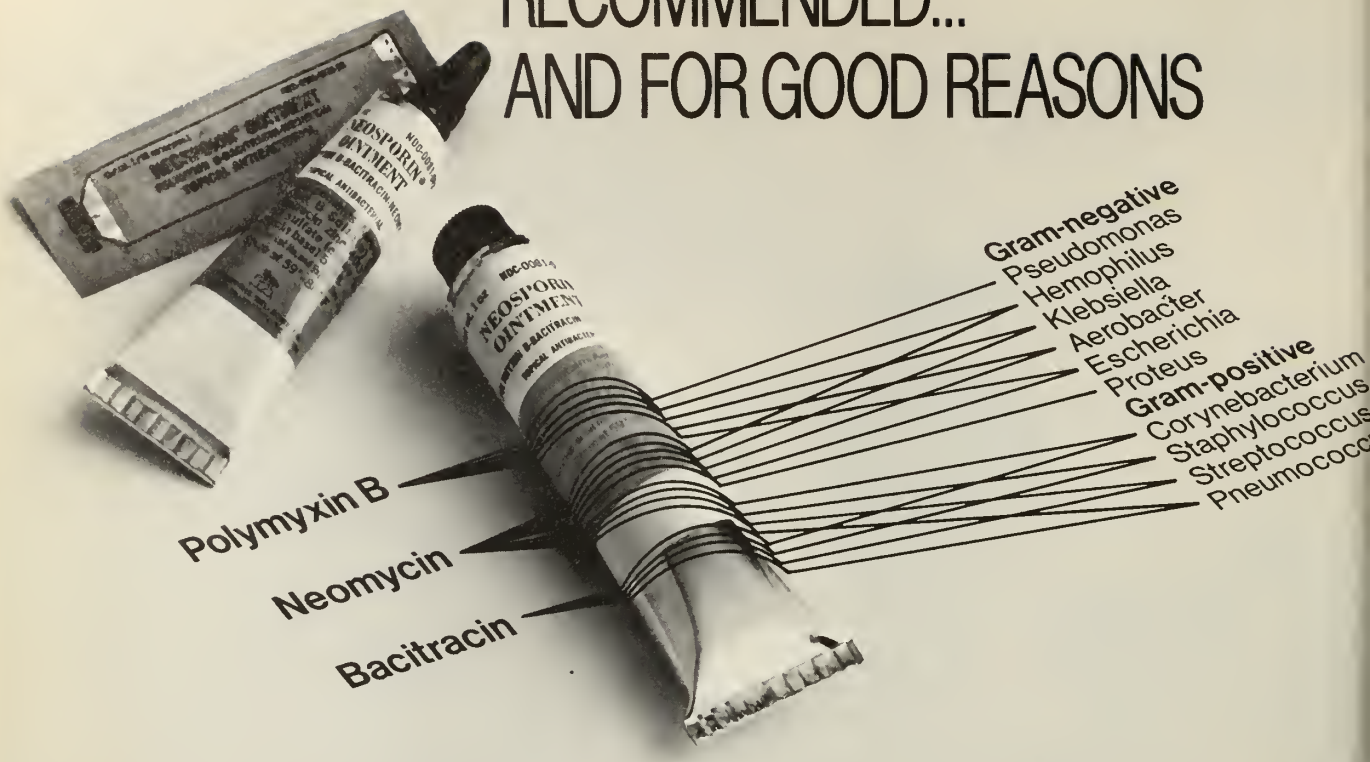
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in the incidence of appendicitis. We did not find such a grouping of cases in our survey for late November, nor for that matter late December. However, we should take into consideration that usually these holiday meals are fairly well balanced with ample portions of unrefined vegetable foods in addition to the goodies. Similarly, there is no peak at Halloween which is the junk food orgy of the pediatric set. Only two each of these holidays are included in this series and perhaps for statistical significance a larger survey should be performed.

These studies should certainly be extended to a classic prospective controlled study. Eliminating one of the major surgical diseases of our time would certainly be a landmark accomplishment. However, we see an insurmountable problem in such a study and that is, we do not know of any population that does not recognize the weekend.

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Albert Ludwig Sigesmund Neisser: 1855-1916—Tribute To A Venerable Physician

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gonorrhea was produced, not syphilis. When he announced this to the world in 1838, however, he refused to believe that gonorrhea had a specific contagious nature and considered asparagus and beer as predisposing factors.[4] The true origin of gonorrhea was still to be discovered.

Albert Ludwig Sigesmund Neisser was born in 1855 in Schweidnitz, Germany, now Swidnica, Poland. The son of a respected physician, he attended St. Maria Magdalena Humanistic Gymnasium in Breslau, where he was a classmate of Paul Ehrlich. In 1872 his medical studies began in Breslau, where he received his degree in 1877. His teachers included Julius Cohnheim, Rudolf Heidenhain and Carl Weigert.

Neisser had planned to be a specialist in internal medicine, but a dearth of openings for assistants in that field turned him to dermatology. After only two years of study, at the age of 24, he discovered the "micrococcus" which now bears his name, Neisseria Gonorrheae. His paper "Über eine der Gonorrhoe eigenthümliche Micrococcenform" in 1879 is considered a milestone in the literature of venereal disease.[5]

He seemed to be at the right place at the right time. The new field of bacteriology was developing rapidly. Ferdinand Cohn, the botanist, taught him Koch's smear test for the identification of bacteria. Staining techniques were taught him by Cohnheim and Weigert. Abbe's condenser and oil-immersion systems had been added to a new Zeiss microscope. Gram's staining technique would make the identification of organisms easier in 1884, and the ability to inoculate culture medium several years later would allow Koch's postulates to be satisfied.

Neisser later did research on syphillis, leprosy, and lupus until his health began to fail in 1912. A fractured hip, recurrent cystitis, kidney stones, and finally diabetes mellitus led to his demise July 30, 1916.[6]

The incidence of venereal disease continues to increase, and new problems are posed by antibiotic-resistant organisms. In 1920 there were 180 cases/100,000 population; in 1977 the rate had increased to 460 cases/100,000, according to CDC data.[7] Though it is now 100 years since *Neisseria gonorheae* was discovered, the eradication of the disease it causes continues to elude us.

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Fever of Unexplained Origin and Retroperitoneal Calcifications

A Case Study

JACK D. MCCUE, M.D.*

INTRODUCTION

Tuberculosis remains an important cause of fever of unexplained origin (FUO), ranging from nearly one-third of Petersdorf and Beeson's cases in 1961[1] to about ten percent in more recent reports.[2,3] It is diagnosed by culture or pathologic examination of tissues. Its potential cause of FUO is usually suggested by a positive tuberculin test.

A case in which the only clue to the diagnosis of tuberculosis was paralumbar lymph node calcifications, a frequently accepted but rarely proven manifestation of mycobacterial infection, is reported.

CASE REPORT

Two months before admission to Penobscot Bay Medical Center this 42-year-old woman developed a low grade fever recurring at approximately weekly intervals. The fevers gradually came at close intervals, eventually reaching approximately 102°F daily. Two weeks before admission she developed drenching night sweats. She lost eight pounds despite a conscious attempt to maintain her weight. She took no medications and there were no psychiatric symptoms.

Past surgical history included an appendectomy, a tubal ligation and venous stripping. She had enjoyed good health and had no past illnesses. She smoked one pack of cigarettes a day and drank alcohol occasionally. She and her husband own a small restaurant. Family history was not helpful.

Physical examination was totally normal except for a careous tooth which showed no evidence of active inflammation.

Laboratory Studies: Her initial complete blood count (CBC) was normal with a hemoglobin of 12.8, a normal white blood cell count and normal differential. Her sedimentation rate was elevated at 52 mm/hr. Subsequently her hemoglobin fell to 10.3 about three weeks later. Her sedimentation rate, white blood cell count and differential did not change. The red blood cell indices were normal. Multiple urinalyses were normal; SMA-12 was normal. Nine blood cultures, urine cultures, bone marrow cultures, and culture of lymph node biopsy were all negative. Serum protein studies showed a marked elevation of acute phase reactants, consistent with an active inflammatory process such as granulomatous disease, chronic infection, or neoplasia. Carcinoembryonic antigen was negative.

Radiographic studies including a liver scan, barium enema, chest x-ray, intravenous pyelogram, upper gastrointestinal series, and Gallium-67 body scan were negative. A gallbladder series demonstrated gallstones, as did an ultrasound examination. A plain abdominal radiograph showed the presence of extensive paralumbar calcifications (Fig. 1). An electrocardiogram was negative.

Hospital course: She had daily fevers as high as 102 F. Although gastrointestinal symptoms were completely absent, it was thought that a cholecystectomy and search for other intra-abdominal sources of fever were necessary. The operation was uneventful. The gross and histologic pathology examination showed chronic cholecystitis with cholelithiasis; a culture of the gallbladder bile was omitted by error. After her operation she once again became



Fig. 1. Bilateral retroperitoneal calcifications are noted (arrows). The calcifications are typical lymph nodes but adrenal calcification may be present as well.

febrile. A biopsy of a posterior cervical lymph node, one centimeter in diameter, was done, and the histology showed a nonspecific inflammatory pattern. Other tissue specimens included a normal bone marrow, a normal needle and wedge liver biopsies. Intermediate PPD and mumps skin tests were negative.

The patient was discharged home to observe her temperature. She continued to have nightly fevers up to 103 F. She returned to the hospital two weeks after discharge, over three months from the onset of her illness. She had no new symptoms. Once again she had a normal physical examination except for the abnormal tooth. An oral surgeon thought the tooth was not the source of her fever, but believed that it should be extracted to exclude it as a potential, albeit unusual, cause.

Laboratory data during this admission included a hemoglobin of 11.3 but otherwise normal CBC; the sedimentation rate was once again elevated at 58 mm/hr. Urinalysis was normal; SMA-12 was normal. Two blood cultures were negative. A culture of the curetting of the tooth extraction site grew *Streptococcus viridans*, and the pathology specimen showed granulation tissue. A Gallium-67 body scan was once again normal. Her second intermediate PPD was negative, but a streptokinase-streptodornase skin test was reactive. She was sent home to take a two-week course of oral penicillin for a presumed tooth infection. She returned to the hospital six weeks later with a recurrence of fever up to 105 F.

Third hospital admission (six months after onset of illness): The patient's history was negative; physical examination revealed no abnormalities. She was also seen in consultation by an ophthalmologist, hematologist, gynecologist and otolaryngologist with negative examinations. Her CBC showed with a hemoglobin of 12.3, normal red blood cell indices, a normal white blood cell count and differential. Her sedimentation rate was 30 mm/hr. Urinalysis was negative; SMA-12 was normal. A lumbar puncture was normal, including a negative culture for tuberculosis, fungi

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and bacteria. A bone marrow biopsy gave negative pathology and culture results. Seven blood cultures were negative. Brucella and rickettsial antibody tests were negative. Serum protein studies once again showed a markedly active inflammatory process. Sinus radiographs showed hypoplastic maxillary antra which were normal by a Gallium-67 scan. A third Gallium-67 body scan was negative. Chest x-ray was negative. The third intermediate PPD was negative. Histoplasmosis (yeast and mycelial), blastomycosis and coccidiomycosis complement fixation titers were negative.

Because of a history of raw milk ingestion as a child, the striking calcification of adrenals and paralumbar lymph nodes, and absence of any other possible source of fever, the patient was started on a therapeutic trial of isoniazide 300mg a day and ethambutol 800mg a day. Three weeks after starting antituberculous medication (nine months after the illness began), she became afebrile, gained weight and felt well. Her sedimentation rate fell to 1 mm/hr, her hemoglobin returned to normal, and her serum proteins showed no evidence of an inflammatory process. A second strength PPD showed mild erythema, but no induration.

Discussion

The evaluation of an FUO, usually defined as a fever of over 101 F for greater than three weeks with no apparent diagnosis after one week of investigation,[1] does not lend itself to a "cookbook" approach. In our age of "explicit branching logic," "algorithms" and "minimum standards" for the evaluation of clinical problems, an FUO is still best diagnosed by chasing clues. After the basic laboratory tests are done (chest x-ray, urinalysis and culture, two to six blood cultures, liver and renal function tests, tuberculin skin tests) further testing should be dictated by clues in the history and physical, and initial laboratory abnormalities.

Radiologic procedures may localize the cause of an FUO without the risk of invasive procedures, but are rarely helpful in the absence of a leading symptom or laboratory abnormality. Upper gastrointestinal series, barium enema, intravenous pyelogram, liver scan, or brain scan are likely to be useful only by excluding illness, since if there is no specific indication by history or physical they will nearly always be normal. One possible exception is the Gallium-67 body scan which has the enormous advantage of revealing areas of occult inflammation.[4] It was not helpful in our patient, but experience with Gallium-67 scans in tuberculosis is limited.

While invasive procedures such as laparotomy, arteriography, and biopsy of liver or lymph nodes may ultimately define the cause of an FUO, they should follow non-invasive studies, and are most likely to be abnormal when physical findings, symptoms, or non-invasive studies point to a particular organ system. A liver biopsy, for instance, is most likely to be abnormal if the liver is enlarged; liver function tests, abnormal in a wide variety of illnesses, are poor predictors of an abnormal liver biopsy.[5] Bone marrow aspiration[1] or lymphangiography[6] are rarely helpful and are useful primarily in evaluation in degree of involvement of a known disease, such as malignancy. The data on the value of laparotomy are controversial. Early reports were encouraging, yielding a high percentage of diagnoses even in patients with no indication of abdominal disease.[7,8] Other investigators using newer non-invasive diagnostic techniques, advise against laparotomy without indications of abdominal disease.[9]

It is ironic that, despite an elaborate evaluation, the only test which indicated the source of the FUO was a plain film of the abdomen, obtained during an intravenous pyelogram, demonstrating extensive retroperitoneal lymph node and adrenal calcifications.

Tuberculosis as a Source of Occult Fever

Tuberculosis is uncommon in Maine. Nevertheless, up to a half dozen cases of active tuberculosis are admitted to our 100-bed hospital yearly. It is likely that tuberculosis as a cause of FUO in this state falls in the lower range of reported figures (about 10%) rather than the upper range (about 30%) reported from large studies in metropolitan areas.

When tuberculosis presents as a FUO it is usually either as primary or reactivated pulmonary disease, or as disseminated tuberculosis. Abdominal tuberculosis is unusual in this country, although it is commonly encountered in India.[10] Ingestion of *Mycobacterium tuberculosis*, such as still commonly occurs in India, may cause abdominal organ involvement without hematogenous dissemination from advanced pulmonary disease, but ingestion of *Mycobacterium bovis* causes most abdominal tuberculosis seen in the United States. Persons inhabitating rural areas before the commonplace tuberculin testing of dairy cattle may have been exposed to *M. bovis*. Persons who have not been exposed to raw milk from such herds, or who live in urban areas, are more likely to be infected with *M. tuberculosis*. The patterns of disease, whether respiratory, disseminated, or abdominal, are no different in *M. bovis* and *M. tuberculosis* infection. The positivity of skin tests, ease of culture, and response to treatment are likewise similar.

Calcified retroperitoneal lymph nodes or adrenal glands are said to be typical of old gastrointestional tuberculosis, brucellosis, histoplasmosis or other mycotic infections. The justification for this assumption, however, is hard to establish: a search of the radiologic literature revealed no series which studied diagnoses represented by this radiologic abnormality. The literature describing radiologic findings in abdominal tuberculosis mentions calcification of lymph nodes in almost every region of the body, but rarely paralumbar calcifications. There are case reports of patients with abnormal retroperitoneal lymphangiographic findings in tuberculosis,[11-13] but no series of cases. A case of fatal paralumbar tuberculous lymphadenitis with a negative intermediate PPD has been reported,[14] too early in the course of the disease to result in calcifications.

The diagnosis of abdominal tuberculosis in the patient described rests on three pieces of data. (1) The history of ingestion of raw milk from non-tuberculin-tested cattle put her at risk for gastrointestional *M.*

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Familial Gastric Lymphoma

ROBERT P. LAURENCE, M.D.*

Familial clustering of malignancy has interested and perplexed physicians for decades. In the search to find the possible causes of cancer, familial clustering seems to bring us closer to an underlying etiology. Little, in 1923, published a report of familial occurrence of cancer in Northern Europe. This was followed by other reports, including Kiedelack's *Heredity in Human Leukemia and Its Relationship to Cancer* in 1947.[1] Since that time frequent reports have appeared describing familial and marital Hodgkin's clustering, familial leukemia, familial lymphoma of the small intestine, and childhood abdominal lymphomas.[2-13] In a thorough search of the English literature, I have no reports describing 1° gastric lymphoma on a familial basis. The following case reports describe such an occurrence and the references offer in depth coverage of familial cancer for the interested reader.



Fig. 1. G.I. series demonstrating lymphocytic lymphoma diffusing involving the fundus and body of the stomach (arrows).

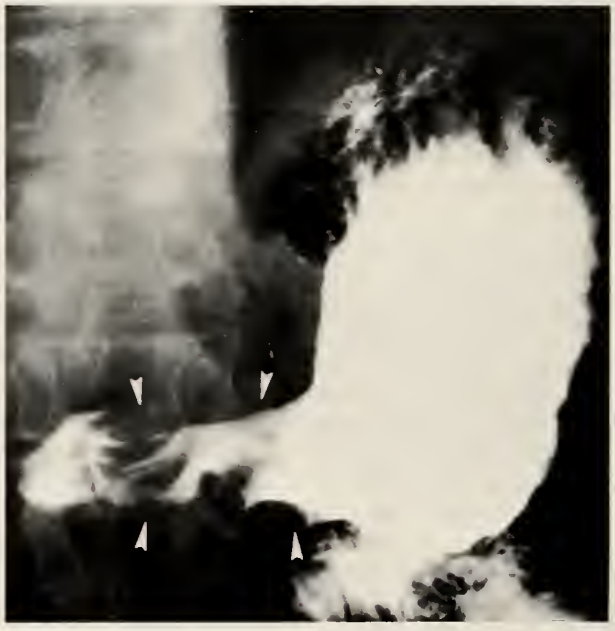


Fig. 2. G.I. series demonstrating histocytic lymphoma involving the antrum of the stomach (arrows).

CASE REPORTS

Case 1 is a 61-year-old male hull caulker with a past history of excessive cigarette and alcohol use, longstanding peptic ulcer disease. On the night of admission to the Penobscot Bay Medical Center, he was in his usual state of health until the acute onset of hematemesis. Vital signs showed a blood pressure palpable at 70, pulse 125. The patient was stabilized and then underwent gastroscopy revealing the site of bleeding to be a ragged area in the distal stomach. UGI was consistent with gastric malignancy (Fig. 1). On the eighth hospital day, the patient underwent high subtotal gastrectomy, splenectomy and appendectomy. The pathology report revealed lymphocytic lymphoma of the stomach; normal appendix and spleen.

Pertinent laboratory data revealed normal bone marrow biopsy and aspirate. Immunoglobulin assay showed normal levels of IgG, IgA, and IgM.

Six weeks post surgery the patient underwent a course of radiation therapy. He is currently asymptomatic.

Case 2 is a 49-year-old male, younger brother of Case 1, who also has a history of peptic ulcer disease 8 years ago, treated with antacids for 6 months. He had no recurrence of symptoms until October of 1978, when he again experienced epigastric pain. UGI (see Fig. 2) revealed a deformity of the distal stomach consistent with gastric malignancy. Endoscopic biopsy revealed gastric mucosa invaded by lymphoma. On the fifth hospital day, the patient underwent gastric resection, splenectomy, appendectomy, and liver biopsy. Pathologic examination revealed histocytic lymphoma of the stomach; normal appendix, omentum, spleen and liver. Bone marrow biopsy and aspirate were normal. The patient has undergone a course of radiation therapy and presently is receiving C-Mopp Chemotherapy. He has continued to lose weight and lack energy.

DISCUSSION

There is as yet no definite etiology linking these cases or other cases of familial lymphoma.

Possible etiologic factors predisposing to familial occurrence are genetic deficiencies, environmental, and infection alteration. Duncan's Syndrome, as described by Purtilo, demonstrates this interrelationship.[14-20] underlying immunodeficiency due to an infections agent (? genetic predisposition) results in progressive loss of T lymphocyte cell function. These T cells govern the proliferation of the B lymphocyte. Challenge in this individual with an agent such as the E-B virus can cause unrestrictive multiplication of the B cells with a B-cell lymphoproliferation disorder.

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Lymphoma itself is not an uncommon disease. Gastric lymphoma is rare however and to see it in two brothers, ages 61 and 49, four months apart suggests more than chance occurrence. How these patients fit in terms of genetics, environment and infections is difficult to say. They, and other members of their families will be watched for evidence of alterations in their immune system, as well as susceptibility to environmental factors.

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Fever of Unexplained Origin and Retroperitoneal Calcifications: A Case Study

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bovis infection. (2) The paralumbar calcification could not be explained on any other basis by history or laboratory studies. (3) The patient's symptomatic response to antituberculous therapy and the correction of laboratory abnormalities were prompt and dramatic after eight months of debilitating illness.

The patient's persistently negative PPD is a troublesome feature of the illness, especially in view of the positive streptokinase-streptodornase skin test. Negative PPD skin tests are found in about 20% of cases of known tuberculosis; most, but not all, such patients have an underlying illness which could explain the negative PPD.[13,14] It is possible that the limited and indolent nature of the patient's tuberculous infection did not stimulate delayed hypersensitivity.

Summary

A patient extensively evaluated for an eight month long fever of unexplained origin (FUO) is described. The only diagnostic clues were calcification of the adrenals and paralumbar retroperitoneal lymph nodes with raw milk ingestion from non-tuberculin-tested cattle as a youth. There was a dramatic and complete response to antituberculous therapy.

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Radiologic Quiz

PETER E. GIUSTRA, M.D., ROGER W. WICKENDEN, M.D. AND PAUL J. KILLORAN, M.D.*

Three weeks prior to admission to the Penobscot Bay Medical Center, a thirty-five-year old male, with a several year history of right ankle discomfort, experienced the acute onset of pain following strenuous activities as a truck driver. He had mild soft tissue swelling about the right ankle medially associated with tenderness over the medial malleolus. Radiographs of the ankle revealed a cystic radiolucency within the medial malleolus (Fig. 1-AP). Ankle arthrogram was negative (Fig. 2-OBL). Ankle bone scan using 99m Tc-pyrophosphate showed increased radioactivity about the right ankle, particularly the medial malleolus (Fig. 3-ANT).



Fig. 1

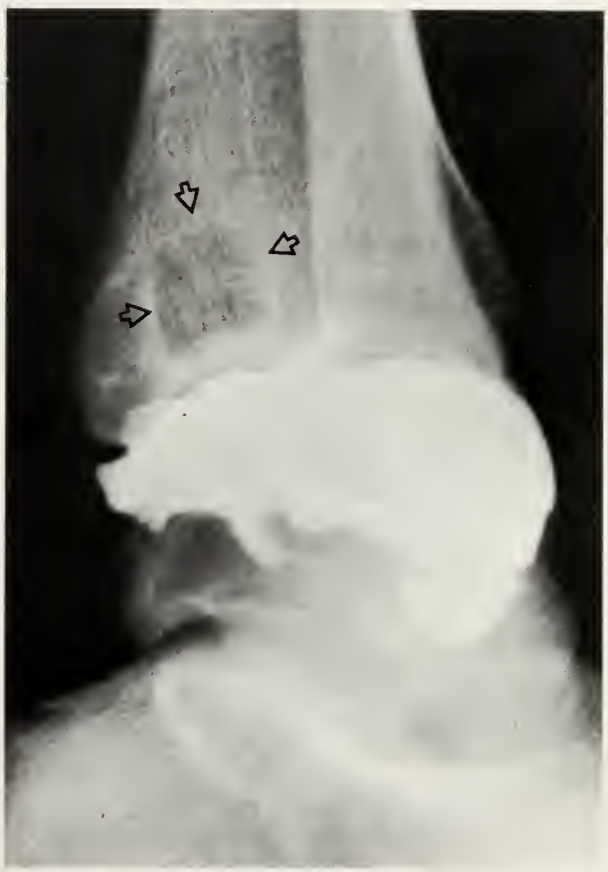


Fig. 2

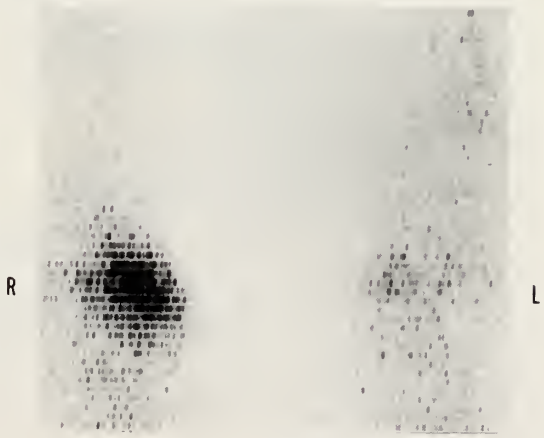


Fig. 3

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For answer see following page

Excisional biopsy with right iliac crest cancellous and cortical bone graft to the right medial malleolus was performed. At surgery, after a window of cortical bone was removed, a well encapsulated cystic cavity filled with viscous yellow material was excised. Surgical and histologic findings confirmed the preoperative radiographic diagnosis of an intraosseous ganglion.

Intraosseous ganglion is a rare lesion of bone but produces a characteristic radiographic appearance, especially when it occurs in the medial malleolus of the tibia.[1,2] The lesion produces a 2-3 cm. rounded cystic radiolucency with a thin sclerotic border, subchondral in location, without calcification or periosteal reaction.

Macroscopically, intraosseous ganglion may communicate with the joint or overlying soft tissue ganglion; but communication via ankle arthrography is presumably a rare finding as we have not encountered a pubished example.

Radionuclide bone scan findings previously have not been reported. It is not clear why the lesion without inflammatory or periosteal reaction would incorporate the 99m Tc-labeled pyrophosphate. The answer may lie somewhere in the work of Kikuchi, et al. "The present histochemical and electron microscopical observations possibly suggest that the immature mesenchymal cells which can produce both collagen fibers and an acid mucopolysaccharide are present within bone or in soft tissue and under the influence of some stimuli may become active and form intraosseous ganglion."[3]

Despite the obscure pathogenesis of intraosseous ganglion and the inability of ancillary roentgenographic procedures such as tomography, arthrography and radionuclide bone scanning to confirm the diagnosis, it is somewhat comforting that this rare lesion of the medial malleolus has a "plain film" radiographic appearance characteristic enough to permit a tenable preoperative diagnosis.

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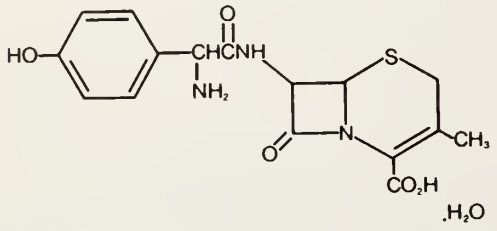
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1. Data on file, Mead Johnson Pharmaceutical Division.
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DESCRIPTION: DURICEF® (cefadroxil monohydrate) is a semisynthetic cephalosporin antibiotic intended for oral administration. It is a white to yellowish-white crystalline powder. It is soluble in water and it is acid-stable. It is chemically designated as 7-[[D-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid monohydrate. It has the following structural formula:



Clinical Pharmacology–DURICEF (cefadroxil monohydrate) is rapidly absorbed after oral administration. Following single doses of 500 and 1000 mg., average peak serum concentrations were approximately 16 and 28 mcg./ml., respectively. Measurable levels were present 12 hours after administration. Over 90 percent of the drug is excreted unchanged in the urine within eight hours. Peak urine concentrations are approximately 1800 mcg./ml. during the period following a single 500 mg. oral dose. Increases in dosage generally produce a proportionate increase in DURICEF urinary concentration. The urine antibiotic concentration, following a 1 gm. dose, was maintained well above the MIC of susceptible urinary pathogens for 20 to 22 hours.

MICROBIOLOGY: *In vitro* tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. DURICEF is active against the following organisms *in vitro:*

Beta-hemolytic streptococci
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Escherichia coli
Proteus mirabilis
Klebsiella species

Note–Most strains of *Enterococci (Streptococcus faecalis* and *S. faecium)* are resistant to DURICEF. It is not active against most strains of *enterobacter species, P. morganii,* and *P. vulgaris.* It has no activity against *Pseudomonas* or *Herella species.*

Disc Susceptibility Tests–Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One recommended procedure (CFR Section 460.1) uses cephalosporin class disc for testing susceptibility; interpretations correlate zone diameters of the disc test with MIC values for DURICEF. With this procedure, a report from the laboratory of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if the infection is confined to the urinary tract, as DURICEF produces high antibiotic levels in the urine.

INDICATIONS: DURICEF (cefadroxil monohydrate) is indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Urinary tract infections caused by *E. coli, P. mirabilis,* and *Klebsiella* species

Skin and skin structure infections caused by staphylococci and/or streptococci

Note–Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATION: DURICEF (cefadroxil monohydrate) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNING: IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE.)

Any patient who has demonstrated a history of some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exception should be made with regard to DURICEF (cefadroxil monohydrate).

PRECAUTIONS: Patients should be followed carefully so that any side-effects or unusual manifestations of drug idiosyncrasy may be detected. If a hypersensitivity reaction occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

DURICEF (cefadroxil monohydrate) should be used with caution in the presence of markedly impaired renal function (creatinine clearance rate of less than 50 ml/min/1.73M²). (See Dosage and Administration.) In patients with known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy.

Prolonged use of DURICEF may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

USAGE IN PREGNANCY: Although no teratogenic or anti-fertility effects were seen in reproductive studies in mice and rats receiving dosages greater than the normal human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

ADVERSE REACTIONS: Gastrointestinal–The most frequent side-effect has been nausea. It was infrequently severe enough to warrant cessation of therapy. Administration with food decreases nausea and does not decrease absorption. Diarrhea and dysuria have also occurred.

Hypersensitivity–Allergies (in the form of rash, urticaria, and angioedema) have been observed. These reactions usually subsided upon discontinuation of the drug.
Other reactions have included genital pruritus, genital moniliasis, vaginitis, and moderate transient neutropenia.

DOSAGE AND ADMINISTRATION: DURICEF (cefadroxil monohydrate) is acid stable and may be administered orally without regard to meals. Administration with food may be helpful in diminishing potential gastrointestinal complaints occasionally associated with oral cephalosporin therapy.

Adults–For urinary tract infections the usual adult dosage is one gm. (two 500 mg. capsules) two times per day. For skin and skin structure infections the usual dose is 500 mg. two times per day or 1 gm. once a day.

In patients with renal impairment, the dosage of cefadroxil should be adjusted according to creatinine clearance rates to prevent drug accumulation. The following schedule is suggested. In adults, the initial dose is 1 gm. of DURICEF (cefadroxil monohydrate) and the maintenance dose (based on the creatinine clearance rate [ml/min/1.73M²]) is 500 mg. at the time intervals listed below.

Creatinine Clearances	Dosage Interval
0-10 ml/min	36 hours
10-25 ml/min	24 hours
25-50 ml/min	12 hours

Patients with creatinine clearance rates over 50 ml/min may be treated as if they were patients having normal renal function.

Children–Dosage and safety have not yet been established in children.

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U.S. Patent Re. 29,164

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Pasturella Multocida Meningitis

JACK D. MCCUE, M.D.*

ABSTRACT

A case of *Pasturella multocida* meningitis in an adolescent presenting with coma and increased intracranial pressure is discussed. Presumably, the illness was contracted by handling a sick rabbit. The patient survived without sequelae.

INTRODUCTION

Pasturella multocida, a common bacterial pathogen in veterinary medicine, rarely causes human illness, and even more rarely, meningitis. A case of *P. multocida* meningitis contracted by hand contact with a sick rabbit is reported. Despite the ominous presentation of coma with a very high cerebrospinal fluid pressure, the patient survived with no evidence of brain damage. Fewer than 25 cases of pasturella meningitis, regardless of variety, have been reported in the medical literature.

CASE REPORT

A 16-year-old girl was admitted to the Penobscot Bay Medical Center after three hours of fever and coma. Three days before admission she had nasal congestion and a mild sore throat. On that day she visited a pet store where she held and played with a rabbit with a "drippy nose and watery eyes." Two days before admission her symptoms of a viral upper respiratory infection were unchanged. One day before admission she had a fever of over 101 F, a left earache, and generalized throbbing headache, and three episodes of vomiting. On the day of admission the headache worsened, her neck felt stiff, and she vomited once again. Her physician noted an inflammed left tympanic membrane, no meningismus, a temperature of 101.2 F, and drowsiness. Within a few hours she became comatose and was referred for admission.

Past medical history, social history and family history were negative.

Physical examination revealed a comatose girl responding to deep pain with purposeless movements. She had random roving eye movements, dyconjugate gaze, hyperactive but symmetrical reflexes, bilateral Babinski reflexes, and a red left tympanic membrane with no evidence of increased middle ear pressure. Fundi were normal as was the remainder of the examination.

A lumbar puncture had an opening pressure of 40cm of water with grossly cloudy cerebrospinal fluid (CSF). The CSF white blood cell (WBC) count was 18,600 with 90% polymorphonuclear leukocytes (PMN'S). The CSF protein was 1.02 gm% and the sugar was 12 mg% (blood sugar was 176 mg%). A Gram stain of the CSF showed sheets of PMN'S with two encapsulated gram positive diplococci. The peripheral WBC count was 27,300 with 32% immature PMN'S. Sinus, skull and chest radiographs were normal.

Cultures of the CSF and two blood cultures grew *Pasturella multocida* (confirmed by the Maine State Laboratories) sensitive to penicillin and chloramphenicol.

Treatment included "heroic" measures to reduce CSF pressure with 150 gms intravenous mannitol every 12 hours and 60 mg dexamethasone every 6 hours. She was initially treated with 30 million units of penicillin G and 4 grams of chloramphenicol daily because the identification of the organism was based on only two organisms on the Gram stain. When the culture grew *P. multocida*, the chloramphenicol was stopped, and after five days the penicillin was reduced to 20 million units daily, for five more days.

The patient's mental status dramatically improved after 36 hours, and by 60 hours after admission she was normal in all respects except for amnesia of the acute illness. Complete mental status testing revealed no abnormalities. Subsequently, she was returned to school and four months later remains asymptomatic.

Additional epidemiologic data included throat cultures of her dog, four cats, and rabbit which were all negative for *P. multocida*. The sick rabbit at one of the local pet stores was one of thirty rabbits sold during the Easter season and could not be traced. Consultation with a local veterinarian revealed that the rabbit farm which supplied the pet store had endemic pasturellosis, with occasional epidemics responsible for many rabbit deaths in the past.

DISCUSSION

Epidemiology

Pasturella multocida is a small encapsulated bipolar-staining gram negative rod. It was first isolated in 1878 by Kitt and 2 years later by Pasteur.[1] It is both a veterinary pathogen causing illnesses grouped as hemorrhagic septicemia, and a commensal organism found in the oral and nasal passages of a large variety of animals. Animals possibly affected include house pets such as dogs, cats, and rabbits; farm animals such as cattle and swine; and wild animals such as lions, rodents and fowl. While *P. multocida* may cause a fatal fulminant illness in unhealthy animals, it also has been cultured from the nasal and oral passages of a majority of healthy domestic dogs and cats.[1] Other potentially pathogenic members of the Pasturella genus include *P. hemolytica, P. ureae, P. tularensis, P. pestis,* and *P. pseudotuberculosis.*

The most common human illness caused by *P. multocida* is cellulitis following an animal bite. Less commonly seen are respiratory infections such as sinusitis, mastoiditis and pneumonia. Rarely central nervous system infections such as meningitis and brain abscess occur. Fewer than half of human *P. multocida* infections have proven animal exposure.[1-2] Meningitis, in general, is contracted through either contiguous spread of an organism, *e.g.*, secondary to sinusitis or mastoiditis, presumably from lymphatic drainage to the CNS; or hematogenous spread with seeding of the organism into the meninges, *e.g.*, from a cellulitis.[2] Because bacteremia from meningitis is nearly universal, and because the primary infection such as sinusitis may also cause bacteremia, it is often difficult to distinguish between these two pathogenic mechanisms.

The probable sequence of events which caused the illness described in this patient are (1) *P. multocida* nasopharyngeal colonization of the patient after touching an infected rabbit; (2) establishment of the organism in sinus or pharyngeal tissue which was compromised by a viral upper respiratory infection;

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(3) probable *P. multocida* tubotympanitis; (4) spread from the middle ear to the meninges *via* lymphatic channels. Two recent cases of infants with *P. multocida* meningitis probably represent a similar pathogenesis, with infection transmitted by the lick of healthy dogs carrying the organism.[4,5] Judging from the rarity of reported cases which have evidence of animal bites or cellulitis, this mode of transmission, *i.e.*, mouth-to-nasooropharynx directly or mediated by hand contact, is probably the most common.

The Gram stain may be confusing, as it was in this case. The bipolar staining and the small size of the rod lead to confusion with *Neisseria meningitidis*, a gram negative diplococcus, and *Haemophilus influenzae*, a pleomorphic gram negative rod. The capsule and possibly an inadequate decolorization of the author's own Gram stain (!) caused consideration of *Streptococcus pneumoniae* as the pathogen. These three CNS pathogens are so much more commonly encountered than *P. multocida* that the expectations of the physician may cause him to misread the Gram stain.

The cultural characteristics of *P. multocida* are not likely to confuse the bacteriologist. It grows well on blood and chocolate agar, but not on media selective for gram negative organisms such as MacConkey's agar. The colonial characteristics and biochemical tests clearly distinguish it from *N. meningiditis, S. pneumoniae,* and *H. influenzae.*

Treatment

The treatment of choice is 12-24 million units of intravenous penicillin G per day. In cases of proved penicillin allergy, chloramphenicol would be the best substitute. Until the sensitivities are done (within 36 hours in this case), addition of chloramphenicol covers for *H. influenzae*; the chloramphenicol should be stopped when bacteriologic sensitivity to penicillin has been demonstrated.

In gravely ill patients with meningitis caused by Gram negative rods other than the pasturellae or *H. influenzae*, intrathecal or intraventricular aminoglycosides are required.[6] Exposure to sick animals, careful definition of the organism as an ovoid small gram negative rod with bipolar staining, and the absence of factors which would predispose to gram negative rod meningitis might allow the physician to delay aminoglycosides 24 hours until it is determined whether the organism grows on gram negative selective media, if the patient is clinically stable.

Increased intracranial pressure required aggressive therapy since fatal brainstem compression from cerebellar or cerebral herniation can occur within a few hours. The usual methods of treating patients with a high CSF pressure include osmotic diuresis with mannitol and large doses of intravenous costicosteroids;[7] which method is more effective in treating increased intracranial pressure in bacterial meningitis is not known.

Prognosis

The unfavorable prognostic factors determining survival in bacterial meningitis include advanced age, coexisting illness, delay in instituting treatment, coma and increased CSF pressure.[2] The latter two apply in this case. The extraordinarily high CSF white blood cell count and protein concentration have no prognostic significance. The mortality of this infection appears to be about 50%.[3]

Acknowledgements

I thank Dr. Gregory O'Keefe of Vinalhaven, Maine for referring the case described.

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Bilateral Endophthalmitis with *Streptococcus Viridans* Endocarditis

JACK D. MCCUE, M.D.* AND ROBERT J. DREHER, M.D.**

ABSTRACT

A 47-year-old man presented with bilateral blindness from endophthalmitis due to bacterial endocarditis. This rare complication of endocarditis has been infrequently reported in *Streptococcus viridans* infections. Treatment includes topical ocular corticosteroids in addition to parenteral antibiotic therapy.

INTRODUCTION

Metastatic endophthalmitis has been described in ophthalmologic literature as a complication of septicemia and acute bacterial endocarditis, and in the medical literature as a complication of pneumococcal and staphlococcal septicemia. It is, however, a rarely encountered complication of endocarditis. Endophthalmitis requires treatment in addition to that of the primary illness. A case of *Streptococcus viridans* endocarditis presenting with endophthalmitis is presented below.

CASE REPORT

A 47-year-old welder was admitted to the Penobscot Bay Medical Center for his first hospitalization with blindness and fever. Three months before admission he stopped working because of generalized weakness and joint aches. One day before admission he noticed visual blurring in the right eye which progressed to blindness over several hours, followed by virtually complete blindness in the other eye.

His past medical history except for heavy consumption of alcohol and cigarettes was negative. A routine eye exam done seven months earlier revealed a 20/30 OD and 20/25 OS acuity and normal visual fields.

Examination on admission showed a thin, dehydrated, acutely ill man with a temperature of 104, a 1-2/6 rough systolic ejection murmur thought to be a flow murmur related to the fever.

Ophthalmologic examination: Vision was light-perception-only OD and finger-counting OS. Schiotz tension was 7/5.5 OU. A severe uveitis was present OU with no view possible of the right retina even with indirect ophthalmoscopy; the left retina showed hemorrhages, cotton wool spots and edema. Numerous white blood cells were seen in the anterior chambers and vitreous.

Laboratory data: The white blood count was 22,600 and the hematocrit was 38%. Sedimentation rate was 40mm per hour. Urinalysis showed 1+ albumin and 2+ hemoglobin with 5 white cells and 5 red cells per high power field. The bilirubin was 1.5 mg% (normal up to 1.1), SGOT was 68 mg% (normal up to 24) and the albumin was 2.4 gm%. Immunoglobulins were normal; rheumatoid factor and antinuclear antibody were borderline at 1:32 and 1:640, respectively. A lumbar puncture had normal pressures, 49 polymorphonuclear leukocytes in the first and third tubes, a low glucose of 50 mg% (peripheral blood sugar 120 mg%) and an elevated protein of 94 mg%; Gram stain, tuberculosis, bacterial and fungal cultures of the CSF were negative. A repeat lumbar puncture done three days after the institution of antibiotic therapy showed 13 white cells in the first tube and 20 white cells in the fourth tube, a protein of 48 mg%, and a sugar of 76 mg%. Anterior chamber paracentesis showed polymorphonuclear leukocytes; stains and cultures were negative for bacteria and fungi.

Hospital course: The patient was treated with ampicillin 1 gram every six hours and gentamicin 80 mg every eight hours IV for presumed bacteremia.

On the second hospital day, showers of petachiae progressively covered his entire body including palms and soles. On the seventh hospital day, a new 2/6 mitral regurgitation murmur was heard and persists to the present time, eighteen months later.

After two of the six blood cultures were reported positive for *S. viridans*, the ampicillin was changed to penicillin G 5 M units every six hours and was continued for a total of six weeks; the gentamicin was discontinued after two weeks. Complicating his hospital course was an episode of delirium tremens which lasted three days in this known heavy beer drinker.

Ophthalmic treatment: The patient was given parenteral methylprednisolone in tapering doses starting at 160mg per day IV, polymyxin-bacitracin-neomycin (Neosporin®) drops and prednisolone acetate 1% with atropine 1% eye drops. Improvement was seen after three days and continued until discharge when his vision was 20/30 OS and 10/25+ OD. Examination at that time showed vitreous haze and two retinal hemorrhages with white centers, and cotton wool. Close out-patient follow-up was necessary because of several recurrences of the iritis OD requiring topical steroids, even eighteen months after cure of the bacterial endocarditis.

DISCUSSION

The general medical literature on infective endocarditis does not mention metastatic endophthalmitis as a complication of bacterial endocarditis.[1-3] Comprehensive reviews of the neurological complications of bacterial endocarditis mention iridocyclitis and panophthalmitis in *acute* bacterial endocarditis referenced to a text book published in 1948,[4] retinal artery emboli and hemorrhage, and cortical blindness.[5] The recent ophthalmologic literature is no more helpful: most cases of metastatic endophthalmitis recorded are secondary to septicemia with pneumococci, beta-hemolytic streptococci, gram negative bacteria, fungi, and tuberculosis.[6,7] Friedenwald[8] in 1930 and Dienst and Gartner[9] in 1944 described several cases of endophthalmitis associated with *S. viridans* endocarditis in autopsy findings. Before penicillin was available, bacteral endocarditis was nearly always fatal, and these cases represent advanced illness rarely seen now.

The difficulty in culturing organisms from the eye in endophthalmitis suggests that along with cotton wool spots, white central retinal hemorrhages, petechiae, and Osler nodes, endophthalmitis due to endocarditis may be an immunologic rather than a metastatic bacterial complication. On the other hand, the presence of intraocular antibodies,

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especially in a chronic systemic infection, may make cultures negative even when bacteria are present.[10] No clinical difference is noted between culture-positive and culture-negative cases.[6,7] Possibly more vigorous attempts at culturing, such as vitreous aspiration, would yield more positive cultures.

Endophthalmitis has many names in the ophthalmologic literature: ophthalmia lenta, septic choroiditis, acquired uveitis, ocular syndrome of SBE, septic retinitis, metastatic endophthalmitis. The ocular inflammatory changes, well described in autopsy studies,[9] include the retinitis described by Roth in 1872, choroiditis, papillitis, and neuritis. The white-centered hemorrhages seen in infective endocarditis which are called Roth spots are not the cotton wool spots (cytoid bodies or soft exudates) described by Roth.[12]

Immunologic incompetence[6] (our patient had normal immunoglobulin levels) and alcoholism (present in our patient) are predisposing factors in the development of endophthalmitis.

Therapy: Endophthalmitis requires corticosteroid therapy because vision may be permanently lost despite appropriate treatment of the underlying infection.[11] In our case, even though the endocarditis was cured by antibiotics, the patient's vision repeatedly deteriorated when ocular steroids were stopped, even up to eighteen months after discharge from the hospital. Aronson, et al[6] found that in bilaterally similar endophthalmitis the eye treated with topical steroids recovered vision better than one treated only with antibiotics. No additional antibiotic treatment other than that given systemically for the primary infection is required.

One unanswered issue in therapy is whether periocular or retrobulbar steroids should be used in addition to the topical medications to assure adequate intraocular levels. The use of IV corticosteroids is not addressed by the literature: in our case their use was prompted by the severity of the endophthalmitis.

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Somatopsychics—Its Relationship to Today's Mental Health

FRANK W. KIBBE, M.D.

The medical profession, the press and the laity in general are very conscious of the meaning of psychomatics and its role in disease. One needs no definition nor explanation of its ramifications in today's society. For want of a better term and because no specific dictionary word is available, I suggest using somatopsychics to describe the reverse entity: the mental impact of physical illness. Often a disease produces profound and sometimes permanent mental changes.

For medical students under the full caloric output of Freud, Jung and Adolph Meyer, as well as the clinical research of Wolf & Wolf, it may come as a surprise that psychobiologic integration is a two-way street. Even though grandmothers are still certain that "little Johnny is unliveable, probably because he has worms," we, as physicians, have not translated this concept into the somatic ills of the elderly.

Recently, while exploring the presence (or absence) of prevention in the state's mental health programs, I found that many of the psychologists and staff members in the mental health clinics are very conscious of aberrations in mental health resulting from physical or somatic traumas. These workers seem to stress "prevention," in the high-risk population. This high-risk group may include in the context of emotional turmoil, the single parent, divorced or separated couples, etc. but equally high-risk are those with: recently discovered tumors, new diabetes or disabling arthritis. The whole adolescent problem turns out to be a mixed bag: emotional conflict, plus incredible hormonal changes, making it as much a physical disease as is menopause.

While many psychiatrists deny the effectiveness of any prevention program in mental health, we are of the opinion that selected programs in education, for patients with somatic ills which frequently lead to emotional difficulties, would be a sound undertaking. Baseline controls in such narrow areas could be meaningful. Once the validity of such education is established the program could be extended to the high-risk situations of the elderly.

R.F.D. 2, Lincolnville, Maine 04849

News, Notes and Announcements

Minutes

The charter meeting of the Maine Society for the History of Medicine was held at the Penobscot Bay Medical Center at 2:00 p.m. on Saturday, November 3, 1979. Twenty-six interested prospective members were present.

Temporary chairman Richard Kahn, M.D., read a Statement of Purpose for the organization, and the group voted to establish the Society.

A short recess allowed those present to read the proposed constitution and bylaws. After a brief discussion, these were adopted.

It was moved and seconded to empower the temporary chairman to appoint a nominating committee which will present a slate of officers at the next meeting.

After a brief discussion of procedural matters and possible future topics and programs, the meeting was adjourned. Dr. Richard Kahn addressed the group on The Development of the Hospital as an Institution.

The next meeting will be held on Saturday, January 26, 1980 at 2:00 p.m. at the Maine Maritime Museum in Bath, Maine. Dr. Charles Burden will speak about nautical medical history.

NOTICE

The newly organized Maine Society for the History of Medicine will meet on Saturday, January 26, 1980 at 2:00 p.m. at the Maine Maritime Museum, Winter Street, Bath, Maine. Dr. Charles Burden will speak on the subject of nautical medical history. Those interested are urged to come and become charter members of the Society.

BILATERAL ENDOPHTHALMITIS WITH *STREPTOCOCCUS VIRIDANS* ENDOCARDITIS

Continued from Page 464

compromised host. *N Engl J Med* 299:130-132, 1978.
11. Baum, J.L., Rao, G.: Treatment of postcataract bacterial endophthalmitis with periocular and systemic antibiotics and corticosteroids. *Trans Am Acad Ophth* 81:151-162, 1976.
12. Lessells: Case records of the Massachusetts General Hospital. *N Engl J Med* 197:492-500, 1977.



CONTINUING MEDICAL EDUCATION IN MAINE

Conferences and Workshops

Hospital Activities

Augusta General Hospital
Augusta, Maine

Jan. 22, 1980: **Tumor Conference**
7:30-8:30 a.m.

Jan. 29, 1980: **Hypertension (Newer Rx?)**
7:30-8:30 a.m. Paul Parker, M.D., Maine Medical Center

These programs have been certified AMA Category I and AAFP (prescribed). For further information contact Mrs. Nancy Favorite; 623-4711. These programs may be viewed over ITS.

Charles A. Dean Memorial Hospital
Greenville, Maine

Jan. 18, 1980: **Renal**
9:30-11:30 a.m. John Engle, M.D., MMMC

This program has been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621.

Eastern Maine Medical Center
Bangor, Maine

Every Mon.	EEG Conference	12-1 p.m.
Every Mon.	Surgical Service—Chief's Rounds	5-6 p.m.
4th Mon.	ENT Section Meeting	12-1 p.m.
4th Mon.	Neurosurgery Section Meetings	4-5 p.m.
3rd Tues.	Dermatology-Pathology Conference	5-6 p.m.
3rd Tues.	Dermatology Section Meeting	6-7 p.m.
4th Tues.	Pulmonary Medicine Section Meeting	8-9 a.m.
1st Wed.	Hematology/Oncology Meeting	8-9 a.m.
Every Wed.	Tumor Clinic Conference	2-5 p.m.
Every Wed.	Radiology Conference (1) Ultrasound/Nuclear Medicine (2) Radiology Film Review (3) Neuroradiology (4) Teaching File Conference	5-6 p.m.
1st Thurs.	Ophthalmology Section Meeting	7:30-8:30 a.m.
	OB-GYN Conference (1) Pathology (2) GYN Analysis (3) OB-Pediatric Combined (4) In-Service and Education	8-9 a.m.
Every Thurs.	Pediatric Grand Rounds	9-10 a.m.
Every Thurs.	Medical Service Conference	10-11 a.m.
Every Thurs.	Cardiology Conference	11 a.m.-1 p.m.
2nd Thurs.	Orthopedic Grand Rounds	7:45-8:45 a.m.
4th Thurs.	Orthopedic Service Meeting	7:30-9 a.m.
4th Thurs.	Surgical Service Death Review	7:45-8:45 a.m.
Every Thurs.	Psychiatric Service Grand Rounds	10-11 a.m.
4th Thurs.	Urology Section Conference	7:30-8:30 a.m.
Every Fri.	Neurology Grand Rounds	8-9 a.m.

Visiting Professor Program:

2nd Thurs.	Medical Service Visiting Professor	10 a.m.-5 p.m.
2nd Thurs.	Anesthesia Service Visiting Professor	7-8 a.m.
3rd Thurs.	OB/GYN Service Visiting Professor	10a.m.-4p.m.
Saturdays	Surgery Service Visiting Professor	8 a.m.-Noon
4th Thurs.	Pediatric Service Visiting Professor	10a.m.-5p.m.
as scheduled	Orthopedic Service Visiting Professor	
as scheduled	Family Practice Visiting Professor	
as scheduled	Psychiatric Service Visiting Professor	
as scheduled	Radiology Service Visiting Professor	

All activities have been certified AMA Category I. For further information contact James F. Lawsing, III, M.D., Coordinator, Medical Education; 947-3711 Ext. 330.

Henrietta D. Goodall Hospital
Sanford, Maine

Dec. 20, 1979: **Office ENT**
Arnold Katz, M.D., New England Medical Center, Tufts University School of Medicine, Boston, Massachusetts

Jan. 22, 1980: **Peripheral Vascular Disease**
Saul Katz, M.D., Maine Medical Center

These meetings will be held at the Henrietta D. Goodall Hospital's Conference Room at 7:00 P.M. These programs have been certified AMA Category 1 and AAFP Prescribed Credit. For further information contact Melvin Bacon, M.D.; 324-3632.

A. R. Gould Memorial Hospital
Presque Isle, Maine

Jan. 7, 1980: **Acute Renal Failure**
7:30-8:30 p.m. Walter Slamenbaum, M.D., Tufts University School of Medicine, Boston, Massachusetts

Jan. 14, 1980: **Aspirin**
7:30-8:30 p.m. Geoffrey Gratwick, M.D., Eastern Maine Medical Center

The meetings will be held at the Rotary Regional Educational Center at the A.R. Gould Memorial Hospital. These programs have been certified AMA Category I. For further information, contact Marilyn Dean; 769-2511.

Maine Medical Center
Portland, Maine

Every Mon.	Student Technologist Conference	8 a.m.
Every Mon.	Hematology-Pathology Conference	11 a.m.
Every Mon.	Pulmonary Conference	12 Noon

Every Mon.	Pediatric Residents' Conference	1 p.m.
Every Mon.	Anesthesia Formal Resident Lecture	3:30 p.m.
Every Mon.	Surgical-Pathology Review	4 p.m.
Every Mon.	Radiology Journal Club	5 p.m.
1st & 3rd Mon.	Clinical Nephrology Conference	11 a.m.
1st & 3rd Mon.	Hematology-Pathology Conference	12 Noon
3rd Mon.	Eye Conference	11:45 a.m.
Every Tues.	Radiology Residents' Seminar	7 a.m.
Every Tues.	Family Practice Grand Rounds	9 a.m.
Every Tues.	Electrocardiographic Interpretation	1 p.m.
Every Tues.	Psychiatric Grand Rounds	1:30 p.m.
Every Tues.	Anesthesia Formal Resident Lecture	3:30 p.m.
Every Tues.	Surgical Seminar	4 p.m.
Every Tues.	Pathology Slide Seminar	4 p.m.
1st & 3rd Tues.	Radiology-Pathology Conference	12 Noon
1st & 4th Tues.	Neurology Conference	12 Noon
2nd Tues.	Infectious Disease Conference	12 Noon
3rd Tues.	Hematology Conference	12 Noon
5th Tues.	Oncology Conference	12 Noon
Every Wed.	Radiation Therapy Conference	7 a.m.
Every Wed.	Urology Conference	7 a.m.
Every Wed.	Student Technologist Conference	8 a.m.
Every Wed.	Continuing Education Seminar	8 a.m.
Every Wed.	Medical Conference	9 a.m.
Every Wed.	Psychiatric Journal Club	12 Noon
Every Wed.	Cardiology Seminar	12 Noon
Every Wed.	Surgical Grand Rounds	5 p.m.
2nd Wed.	Guest Internist—Medical Conference	9 a.m.
4th Wed.	Medical Mortality Conference	9 a.m.
Alt. Wed.	Neurology-Psychiatry Seminar	11 a.m.
Alt. Wed.	Anesthesiology Journal Club	3 p.m.
Every Thurs.	Thoracic Surgery Conference	7 a.m.
Every Thurs.	OB/GYN Conference	7 a.m.
Every Thurs.	Anesthesiology Clinical Conference	7 a.m.
Every Thurs.	Diagnostic Radiology Teaching Conference	7 a.m.
Every Thurs.	Surgical Conference	8 a.m.
Every Thurs.	Pediatric Conference	9 a.m.
Every Thurs.	Tumor Consultation Board	11 a.m.
Every Thurs.	Medical Resident Conference	12 Noon
Every Thurs.	Surgical Seminar	4 p.m.
Every Thurs.	Endocrinology Conference	5 p.m.
Every Thurs.	Dental Specialty Lecture	6 p.m.
1st Thurs.	Anesthesia Mortality Conference	7 a.m.
1st Thurs.	Guest Pediatrician	9 a.m.
1st & 3rd Thurs.	Gastroenterology Conference	12 Noon
1st & 3rd Thurs.	Cardiac-Surgical Conference	12:30 p.m.
1st, 3rd, & 5th Thurs.	Pulmonary Physiology Conference	12:30 p.m.
2nd Thurs.	Cardiology Teaching Conference	12:30 p.m.
2nd Thurs.	Clinical Anesthesiology Lecture Series	3:30 p.m.
2nd Thurs.	Eye Staff Scientific Session	5:30 p.m.
2nd Thurs.	Maine Medical Center Medical Staff Meeting and Scientific Session	6 p.m.
2nd & 4th Thurs.	Pulmonary-Pathology Conference	12 Noon
2nd & 4th Thurs.	Endocrinology Conference	12 Noon
3rd Thurs.	Combined Guest Physician or Guest Surgeon Program	8 a.m.
3rd Thurs.	Clinical Anesthesiology Lecture Series	3:30 p.m.
4th Thurs.	Surgical Mortality Conference	8 a.m.
4th Thurs.	Anesthesia Mortality Conference	3:30 p.m.
Last Thurs.	Pediatric Mortality Conference	9 a.m.
Every Fri.	Thoracic Surgical Conference	7 a.m.
Every Fri.	Nuclear Medicine Conference	7 a.m.
Every Fri.	Student Technologist Conference	8 a.m.
Every Fri.	Neurological-Neurosurgical Conference	8:30 a.m.
Every Fri.	Gastroenterology Conference	9 a.m.
Every Fri.	Medical Rehabilitation Staff Conf.	9 a.m.
Every Fri.	Orthopedic Conference	9 a.m.
1st Fri.	Dermatology Conference	12 Noon
2nd Fri.	Nephrology Conference	12 Noon
3rd Fri.	Rheumatology Conference	12 Noon
4th Fri.	Oncology Conference	12 Noon
Alt. Fri.	Oncology Radiation Conference	7 a.m.
Alt. Fri.	Gastroenterology Conference	10 a.m.

All programs have been certified AMA Category I. For further information contact Costas T. Lambrew, M.D.; 871-2111.

Mercy Hospital
Portland, Maine

Jan. 8, 1980: 8-9 a.m. — Family Practice Grand Rounds

Jan. 15, 1980: 8-9 a.m. — **Clinical Management of Spinal Anesthesia**
Henry Grant, M.D., Department of Anesthesia, Mercy Hospital

These programs have been certified AMA Category I. For further information contact Harold Pariser, M.D.; 774-1461, Ext. 363.

Mid-Maine Medical Center
Waterville, Maine

Dec. 20, 1979: Case Presentation—Family Practice Residents

Jan. 10, 1980: **Diabetes Mellitus: Adult**
Thomas Flood, M.D., Joslin Clinic, Boston, Massachusetts

Jan. 17, 1980: **Diabetes Mellitus: Juvenile**
Stuart Brink, M.D., Joslin Clinic, Boston, Massachusetts

Jan. 15, 1980: **Asthma in Pregnancy**
Case Presentation—Sanders Burnstein, M.D., MMMC
Discussion—Irvin Paradis, M.D., MMMC

Jan. 22, 1980: **Thyroid Disease in Pregnancy**
Case Presentation—Ann Dorney, M.D., MMMC
Discussion—Herbert Bartholomew, M.D., Augusta General Hospital

Jan. 29, 1980: **Hypertension in Pregnancy**
Case Presentation—Sanders Burstein, M.D., MMMC
Discussion—Speaker to be announced

All programs run from 12-1 p.m. and have been certified AMA Category I and AAFP (elective). For further information contact David Ginder, M.D.; 873-0621. These programs may be viewed over ITS.

Sebasticook Valley Hospital
Pittsfield, Maine

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Frances Dyro, Neurologist, West Roxbury V.A. Hospital
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DIABETES MELLITUS: 1979

A Maine Perspective

NOV 1 3 1979

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INTRODUCTION

For those of us who have been involved in diabetes detection programs for a long time, it is a great pleasure to see the new intensive effort being mounted by this well organized group of young individuals, who, to use the current jargon, are "Putting It All Together."

With adequate staff and funding it might have happened years ago—but it didn't. And so I take this opportunity as Chairman of the Diabetes Committee of the Maine Medical Association to welcome you to the field where we have labored so long, and to offer you our complete cooperation and to wish you well with the Diabetes Program.

We shall be pleased to continue to cooperate and to help with the effort in any way you may desire.

MELVIN BACON, M.D.
27 June Street
Sanford, Maine 04073

Publication of this special supplement was supported in part by the Diabetes Control Project, a joint undertaking of the Maine Department of Human Services and Medical Care Development funded through a contract with the Center for Disease Control, USDHEW. The content of the individual articles are the sole responsibility of the listed authors. They are not in any way to be considered the responsibility of the Maine Department of Human Services, Medical Care Development, or the Center for Disease Control.

Epidemiology of Diabetes in Maine

Pomeroy Sinnock, Ph.D.*

Introduction

A major objective during the first year of the Diabetes Control Project (DCP) was to analyze existing mortality and morbidity data on Maine diabetics. Four major areas of mortality/morbidity were investigated—mortality due to diabetes, diabetic hospitalizations including number of discharges and length of stay, amputations among diabetics, and perinatal mortality in diabetic pregnancies. This paper presents a summary of the health status indicators that will be used in the coming years to monitor changes in mortality/morbidity of Maine's diabetics.

Prevalence and Incidence

Although no specific data on the prevalence and incidence of diabetes in Maine is available, age specific rates derived from the Health Interview Survey of the National Center for Health Statistics can be applied to Maine population data to obtain general estimates of prevalence and incidence. The estimates for Maine, presented in Tables 1 and 2, do not take into account racial, ethnic, or cultural differences. However, such estimates may be useful for local purposes. In 1975, there were an estimated 21,037 diabetics in Maine of which 43% were age 65 and over.

Although there is no general agreement concerning the classification of the different types of diabetes, such as insulin dependent, insulin independent, juvenile onset, and maturity onset, national data[1] indicate that 19% of all diabetics do not rely on any treatment (oral hypoglycemic agents, insulin and/or diet) for control, 21% use insulin, 40% use oral hypoglycemic agents, and 19% are treated by diet alone.

Mortality

Diabetes mortality data were obtained through the Bureau of Research and Vital Records for the years 1973-1977. Diabetes is one of the 10 leading causes of death in Maine ranking sixth in 1973 and 1974, seventh in 1975 and 1976, and ninth in 1977. The data, presented in Table 3, show that the number of deaths with diabetes as the underlying cause of death has decreased by 34% from 1973 to 1977, while deaths from all causes has decreased only 7%. No specific reason for the dramatic decrease in diabetic deaths can be identified but the general improvement in overall medical care in Maine must be considered a factor. A majority (92%) of deaths with diabetes as the underlying cause of death are recorded as "diabetes without mention of ketoacidosis/coma," while the remaining 8% of the deaths are the result of diabetic ketoacidosis/coma (DKA).

During 1973-1977, there were no diabetes deaths in persons less than 15 years of age and only seven deaths (three DKA and four nonDKA) in persons less than 25.

Overall, the diabetes death rate increases with age. Females have 57.5% of the deaths, which is proportional to the frequency of females in the diabetic population.

Table 1

Estimated Prevalence of Diabetes in Maine: 1975

Hospital Service Area	Estimated Number of Existing Cases of Diabetes by Age 0-17	18-44	45-64	65+	Total
1. Bath	7	56	161	158	382
2. Belfast	5	43	113	124	285
3. Biddeford	19	157	424	460	1,060
4. Boothbay	2	15	55	69	141
5. Bridgton	4	31	92	110	237
6. Brunswick	14	120	246	239	619
7. Camden	2	16	58	93	169
8. Damariscotta	2	19	63	93	177
9. Portland	69	567	1,524	1,602	3,762
10. Rockland	11	93	267	354	725
11. Sanford	9	70	196	230	505
12. York	4	36	109	138	287
13. Farmington	9	78	180	194	461
14. Lewiston	38	316	816	885	2,055
15. Norway	5	37	108	125	275
16. Rumford	10	78	208	204	500
17. Augusta	24	201	564	618	1,407
18. Jackman	1	4	11	13	28
19. Pittsfield	5	39	94	106	244
20. Skowhegan	10	82	220	234	546
21. Waterville	22	180	443	463	1,108
22. Bangor	44	366	790	809	2,009
23. Bar Harbor	3	28	87	109	227
24. Blue Hill	3	23	77	113	216
25. Calais	4	33	94	107	238
26. Castine	1	4	9	12	26
27. Dexter	3	23	64	70	160
28. Dover-Foxcroft	3	27	78	91	199
29. Eastport	1	8	28	48	85
30. Ellsworth	6	46	126	159	337
31. Greenville	1	8	28	31	68
32. Lincoln	5	41	97	96	239
33. Machias	5	44	130	168	347
34. Millinocket	5	44	88	62	199
35. Milo	2	12	41	45	100
36. Caribou	6	46	104	80	236
37. Fort Fairfield	6	52	60	45	163
38. Fort Kent	8	62	124	111	305
39. Houlton	6	51	76	146	279
40. Island Falls	2	15	20	38	75
41. Presque Isle	11	89	197	178	475
42. Van Buren	2	16	31	32	81
Maine	398	3,276	8,301	9,062	21,037
Per 1,000 Population	1.2	8.5	40.6	72.3	

*Diabetes Control Project, Medical Care Development, Inc., Department of Human Services, Augusta, Maine 04330.

TABLE 2

ESTIMATED INCIDENCE OF DIABETES IN MAINE: 1973

Hospital Service Area	Estimated Annual Number of New Cases of Diabetes by Age 0-17	18-44	45-64	65+	Total
1. Bath	2	14	23	14	53
2. Belfast	1	11	16	11	39
3. Biddeford	5	38	60	41	144
4. Boothbay	1	4	8	6	18
5. Bridgton	1	8	13	10	32
6. Brunswick	4	29	35	21	89
7. Camden	1	4	8	8	20
8. Damariscotta	1	4	9	8	22
9. Portland	19	137	215	141	512
10. Rockland	3	22	38	31	94
11. Sanford	2	17	28	20	67
12. York	1	9	15	12	37
13. Farmington	2	18	26	17	63
14. Lewiston	11	76	115	78	280
15. Norway	1	9	15	11	36
16. Rumford	3	18	29	18	68
17. Augusta	7	48	80	55	190
18. Jackman	1	1	2	1	4
19. Pittsfield	1	10	13	9	33
20. Skowhegan	3	19	31	21	74
21. Waterville	6	44	63	41	154
22. Bangor	12	88	112	71	283
23. Bar Harbor	1	6	12	10	29
24. Blue Hill	1	5	11	10	27
25. Calais	1	8	13	9	31
26. Castine	1	1	1	1	4
27. Dexter	1	9	9	6	25
28. Dover-Foxcroft	1	6	11	8	26
29. Eastport	1	2	4	4	10
30. Ellsworth	2	11	18	14	45
31. Greenville	1	2	4	3	9
32. Lincoln	1	10	14	8	33
33. Machias	1	11	18	15	45
34. Millinocket	1	11	12	5	29
35. Milo	1	4	6	4	14
36. Caribou	2	11	15	7	35
37. Fort Fairfield	2	12	8	4	26
38. Fort Kent	2	15	17	10	44
39. Houlton	2	12	18	13	45
40. Island Falls	1	4	6	3	13
41. Presque Isle	3	21	28	16	68
42. Van Buren	1	4	4	3	11
Maine	107+	793	1,183	798	2,881
Per 1,000 Population	.3	2.1	5.8	6.4	

TABLE 3

DIABETIC MORTALITY IN MAINE: 1973-1977

	Number of Deaths 1973	1974	1975	1976	1977
Diabetes as underlying cause of death	225	232	196	172	149
Diabetes as a contributing factor	—	—	—	704	530
Total deaths in Maine	10,837	10,705	10,253	10,422	10,055

TABLE 4

AGE-ADJUSTED DEATH RATE* IN THE EIGHT HEALTH PLANNING REGIONS (FIVE-YEAR AVERAGE 1973-1977)

Region	County	DKA	NonDKA
I	York	2.1	20.5
II	Cumberland	1.0	17.6
III	Knox, Lincoln, Sagadahoc, Waldo	1.4	19.2
IV	Androscoggin, Franklin, Oxford	2.7	23.8
V	Kennebec, Somerset	2.1	20.8
VI	Penobscot, Piscataquis	1.2	16.4
VII	Hancock, Washington	1.2	16.3
VIII	Aroostook	1.6	16.4

*Per 100,000 population—based on 1970 Census data.

Age adjusted death rates in Maine for eight health planning regions (see State of Maine Medical Facilities Plan, 1977) are shown in Table 4. Overall, the average death rate for Maine in 1973-1977 was 18.4 per 100,000 persons. In 1976, the crude U.S. death rate was 16.3 per 100,000 persons.

DIABETES MORBIDITY

Hospitalization

Hospital discharge data was obtained from the 100% data file for the years 1974-1976. The estimated 21,000 diabetics in Maine are hospitalized an average of 9,348 times a year and spend a total of 98,310 days in the hospital each year. Of the total patient days, 16.8% are with a primary diagnosis of diabetes, and the remaining 83.2% are for persons having a secondary diagnosis of diabetes. Discharge rates for the eight regions in Maine are presented in Table 5. The average lengths of stay per discharge is presented in Table 6. For comparison, the average length of stay for any discharge in Maine is 6.9 days.

Analysis of the variation in DKA and NonDKA discharge rates between hospital services in Maine showed a little difference for DKA discharge rates when tested statistically. Four areas were significantly greater than the State rate, and one area was significantly lower. Adjusting diabetes discharge rates for differences in age and total discharge rates between areas did not change the outcomes. For Non-DKA rates, however, 14 areas showed significant differences from the State rate. Adjusting for age had no effect on the discharge rates. However, adjusting for age and total discharge rate had a major effect and greatly reduced the number of areas that were significantly different from the State rate. After this adjustment only four areas were significantly different from the State rate (two higher and two lower).

Not all diabetics have the same risk of hospitalization. Table 7 presents the probability of hospitalization for Maine's diabetics by age group. The younger and older age groups, 0 to 17 and 65+, have a better than 50% chance of being hospitalized each year.

Amputations

Of the 637 persons having a toe, foot, or leg amputation in 1975 and 1976, 309 of these or 48.5% had diabetes. Among the diabetic amputations, 36% are toe amputations, 10% foot amputations, and 54%

Table 5

Diabetic Discharge Rates (Per 10,000 Population) in Health Planning Regions of Maine

Region	Primary DX of Diabetes* DKA	Primary DX of Diabetes* NonDKA	Secondary DX of Diabetes**	All-Cause Diabetes	All Discharges any DX***
I	3.1	14.3	100.5	118.8	1,619
II	1.5	13.7	71.3	86.6	1,487
III	2.4	19.2	64.5	87.2	1,605
IV	2.1	16.4	71.4	90.1	1,582
V	3.1	16.6	89.1	109.1	1,880
VI	2.7	11.2	55.8	68.8	1,506
VII	3.2	23.3	87.4	117.0	2,037
VIII	3.0	24.9	60.6	84.5	2,028
MAINE	2.5	16.2	71.9	90.4	1,660

*1974-1976 Average: Age Adjusted
**1975-1976 Average
***1975

Table 6

Average Length of Stay Per Diabetic Discharge in Health Planning Regions in Maine

Region	DKA Discharges	Non-DKA Discharges	Secondary DX of Diabetes	All-Cause DM Discharges
I	9.1	7.8	9.7	9.5
II	8.4	11.5	11.5	11.4
III	5.9	8.2	9.7	9.3
IV	8.1	9.0	11.0	10.5
V	7.7	8.8	10.5	10.1
VI	6.9	8.1	12.5	11.6
VII	6.1	8.3	9.1	8.9
VIII	6.7	8.0	10.0	9.4
MAINE	7.4	9.0	10.9	10.4

Table 7

Probability of Hospitalization for Diabetics in Maine By Age Group: 1975

	0-17	18-44	45-64	65 +	Total
Primary Diagnosis of Diabetes	.394	.105	.073	.080	.087
DKA	.148	.027	.005	.007	.012
NonDKA	.246	.078	.068	.073	.075
Secondary Diagnosis of Diabetes	.166	.189	.300	.442	.341
Total Diabetes	.560	.294	.373	.522	.428

leg amputations. The majority (64%) occur in persons over 65 years of age. Studies[2-3] have shown that the number of amputations in diabetics can be significantly reduced with a comprehensive diabetes care program, that includes emphasis on proper foot care.

Perinatal Mortality

Data on perinatal mortality/morbidity in diabetic pregnancies in Maine is limited. Hospital discharge data identified only about 14% of the estimated 450 diabetic pregnancies in Maine. This data source does not provide information on the outcome of the pregnancies. Birth certificates do not provide reliable estimates because only rarely is the mother recorded as a diabetic on the certificate. No data is available on the diabetic neonatal death rate.

The best data, for the present, is being generated by the Maine Fetal Risk Project through the prenatal scorecard being used by physicians throughout Maine. A preliminary analysis of early returns of these cards indicate that diabetics account for 1.9% of all pregnancies. An estimated 1.1% of these are gestational or Class A diabetic pregnancies and 0.8% are classified prepregnancy or Class B, C, or D diabetic pregnancies. Although the numbers are too small for meaningful calculations, a fetal or neonatal death occurred in 17% of the Class B-D diabetic pregnancies. No mortality was observed in the gestational diabetic pregnancy. A more detailed analysis will be done in conjunction with Maine Fetal Risk Project within the next year and accurate estimates of the magnitudes of perinatal mortality in diabetic pregnancies in Maine will be obtained.

Costs of Diabetic Hospitalization

Utilizing data obtained from the Maine Health Data Service and Maine Blue Cross/Blue Shield to determine the patient day costs for a diabetic

Continued on Page 15

Developing a Diabetes Control Project in Maine

WILLIAM J. CARNEY, M.S.P.H.,* JUSTIN W. COWGER** AND BETH WILLHOITE, M.S.**

National concern about diabetes is reflected in Congressional action of 1974 which established the National Commission on Diabetes to formulate a long-range plan to combat diabetes mellitus. In its report to Congress in December 1975, the Commission found that when diabetes and its complications are considered together, diabetes is the third leading cause of death from disease in the U.S. and significantly decreases life expectancy. Diabetes is one of the ten leading primary causes of death in Maine, and an estimated 21,000 Maine residents are diabetics.

A major recommendation of the Commission was the funding and establishment of a series of state-based, community diabetes control demonstration projects through the Center for Disease Control (CDC). Maine's Department of Human Services and Medical Care Development (MCD) jointly submitted a proposal to CDC in July of 1977 for the purpose of instituting a project in Maine. Twenty-seven states responded to the initial request for proposals and Maine was one of ten states chosen to receive contracts for the purpose of planning and developing activities designed to reduce morbidity and mortality associated with diabetes mellitus. Other states receiving contracts were Colorado, Georgia, Illinois, Michigan, Mississippi, Nebraska, New York, Rhode Island, and South Carolina. Two additional states, Ohio and Washington, were funded in October 1979, and it is anticipated that eight additional states will be funded in 1980.

The Diabetes Control Project (DCP) for Maine receives overall advice and direction from a 21-member advisory committee, representing Statewide health care interests (See Figure 1).

During the initial planning year beginning in October of 1977, major problems of the Maine diabetic population were identified through an analysis of existing diabetes mortality/morbidity data and an assessment of Statewide health care resources available to diabetics. The problems did not indicate misutilization of health services but rather identified areas where early intervention would prevent or substantially delay the disease process from reaching the stage whereby hospitalization or other acute medical service would become a medical necessity. The problem areas included:

—Preventable hospitalizations.
—Preventable perinatal mortality/morbidity in diabetic pregnancies.
—Preventable amputations.
—Preventable blindness caused by unrecognized and/or untreated diabetic retinopathy.

Four primary factors were identified during the first year as contributing to these problems:

1. Lack of coordination and communication among resources delivering medical and educational services to the diabetic, resulting in duplication of effort, confusion to the diabetic, and less than optimum utilization of existing resources.
2. Significant variation in the educational programs provided to hospitalized diabetics, with only a limited number of programs available to nonhospitalized diabetics in Maine. The lack of ambulatory diabetic education programs may contribute substantially to unnecessary hospital utilization.
3. Lack of third-party payment for ambulatory diabetes education and follow-up as a covered outpatient service.
4. Continuing medical education programs in diabetes are uncoordinated, with some areas of the State without any locally available programs.

Based on the specific problems identified among Maine's diabetic population during the second year and the reduction in certain health status indicators achieved by diabetes control programs in Atlanta, Los Angeles, and Memphis, the Diabetes Control Project has now set the following goals to be achieved by 1985. The goals are consistent with the long-term goals set by CDC in their national diabetes control program.

GOAL 1: By 1985, reduce the total number of hospital days among diabetics by 30% by achieving:

—50% reduction in hospitalizations for diabetic ketoacidosis/coma.
—43% reduction in hospitalizations for diabetes without mention of DKA.
—50% reduction in all-cause diabetic hospitalizations.
—30% reduction in the number of amputations among diabetics.

GOAL 2: By 1985, reduce the Statewide perinatal mortality rate in diabetic pregnancies from an estimated 14% to 7%.

GOAL 3: By 1985, reduce the estimated incidence of blindness in diabetics by 10%.

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The Diabetes Control Project is funded under a contract with the Center for Disease Control in Atlanta, Georgia and is a joint venture of Maine's Department of Human Services, Augusta, Maine 04333 and Medical Care Development, Inc., 295 Water Street, Augusta, Maine 04330.

FIGURE 1

DIABETES CONTROL PROJECT ADVISORY COMMITTEE (AS OF AUGUST 1979)

AUSTIN, Roger N., M.D.
Androscoggin County Medical Society

BACON, Melvin, M.D.
Chairman
Diabetes Committee
Maine Medical Association

BAILEY, Laura
Consumer

CARNEY, William J.
Consultant

CARPENTER, Georgette, R.N.
Diabetes Nurse Specialist
Maine Medical Center

HAYNES, Julian, Ph.D.
Assistant to the Coordinator
of Health Science Foundation
University of Maine/Orono

HEGGIE, W. Grant, Jr.
Vice-President
Maine Hospital Association

HUTCHINS, David G., D.P.M.
Maine Podiatry Association, Inc.

LEADLEY, Peter J., M.D.
Medical Director
Pine Tree Organization for
Professional Standards Review, Inc.

MacCRACKEN, Joan, M.D.
Pediatric Endocrinologist

McGINTY, Francis
Deputy Commissioner
Health & Medical Services
Department of Human Services

MANSFIELD, Stephen J.
Maine Health Systems Agency

MERRILL, Jackie, R.D.
Maine Dietetic Association

MILLER, Edward
Director
Health Education Program
Department of Human Services

MULLANE, Michael
Patient Education Coordinator
Health Education Resource Center
University of Maine/Farmington

O'DONNELL, Kathryne, R.N.
Maine State Nurses' Association

RANKIN, Geraldine, R.N.
Maine Health Care Association

SAUNDERS, Norman W., M.D., Chairman
Pine Tree Diabetes Association

WEISENBERG, Jane M.
Director of Training
Regional Approach to In-Service Education

ZINESKI, Stefan, M.D.
State Epidemiologist

VACANCY
Maine Osteopathic Association

In order to reach these goals, a series of objectives has been formulated in five areas.

The first area is the development of a capacity for the planning, coordination, management, evaluation, and surveillance of diabetes in Maine. Existing resources within the Department of Human Services include Statewide health planning capabilities, data systems and data bases, an array of public health programs including nursing services, and regulatory functions. Resources at Medical Care Development include expertise in epidemiological analysis, project development and implementation, and evaluation of health care systems. These combined resources will be organized within the framework of the Diabetes Control Project to achieve an effective management system with the capacity for monitoring and evaluating the long-range impact of DCP activities.

Regional coordinating councils in each of eight diabetes health planning regions will allow for local input of area providers and consumer diabetics into the diabetes plan for their region. Three councils have been formed with the remaining five to be organized in the coming year.

The second area is the development and implementation of ambulatory diabetic education and follow-up (ADEF) programs as an integral part of patient care. (See article on page 7.)

Some institutions/agencies are reluctant to initiate ambulatory education programs that will increase costs, and are not currently reimbursed by third-party payers. The Diabetes Control Project is actively pursuing approval on a pilot basis with Blue Cross/Blue Shield in Maine, Medicaid, and Medicare for inclusion of ambulatory diabetic education and follow-up as a covered outpatient service. A special Education Reimbursement Committee, made up of representatives of the major health organizations in Maine, advises the project in the development of the cost-reimbursement proposal and will approve and recommend its acceptance by third-party payers. A detailed cost benefit projection clearly shows the overall cost reduction potential of this project.

The Diabetes Control Project has set as one of its objectives in the coming year the implementation of a model ambulatory diabetic education and follow-up (ADEF) program in 15 sites throughout Maine.

The third area is coordination and expansion of

Continued on Page 21

Rationale and Description of Model Ambulatory Diabetic Education and Follow-up Program

ROBERT ANDERSON, ED.D.* AND ROBERT GENTHNER, PH.D.**

ABSTRACT

Diabetes Mellitus is a disease that frequently requires substantial behavior change by diabetics to achieve the compliance and control prescribed by their physician. Diabetics must acquire new knowledge, skills, and self-care attitudes to successfully manage their diabetes. To support this effort, comprehensive and effective education programs should be available to physicians for their diabetic patients. Maine is currently working to establish a Statewide system of model Ambulatory Diabetic Education and Follow-Up (ADEF) programs.

INTRODUCTION

The Maine Diabetes Control Project (DCP) is committed to seeing Maine achieve a Statewide reduction in the preventable morbidity and mortality associated with diabetes. The central component of the DCP effort is the development of a model ambulatory diabetic education and follow-up (ADEF) program to be reimbursed by third-party payers as a regularly covered service. This program was designed by the DCP and a Statewide Task Force of Diabetes Educators.

This paper will examine two aspects of the model ADEF program: 1) the rationale for the program's design; and 2) a description of program components.

I. Program Rationale

The DCP is developing a proposal which seeks reimbursement from third-party insurers for hospitals and other health care institutions which sponsor ambulatory diabetic education and follow-up programs. The programs would be required to meet guidelines established by a Statewide Task Force of Diabetes Educators.

The major thesis of the DCP's reimbursement proposal is that a well designed, high quality, and comprehensive ADEF program taught by a qualified, trained, and motivated staff will have a significant impact on the quality of self-care undertaken by diabetics, their friends, and families. The program will be evaluated in terms of improved compliance and control resulting in a reduction of preventable diabetic morbidity, mortality, and unnecessary utilization of expensive hospital services.

A well designed education program will impact on the following learning domains: knowledge (cognitive), skills (psychomotor), and attitudes (affective). An examination of the design of many national diabetes education programs shows that their focus is almost entirely on the knowledge and skills domain. These programs lack a systematic approach to achieving positive self-care attitudes. As a consequence, a substantial number of health care providers in Maine and nationally continue to report that many diabetics lack the motivation, skills, and knowledge for effective self-care.[1-6]

The model program designed for Maine is a comprehensive approach to providing knowledge and skills with a coordinated approach to influencing attitudes. The model ADEF program is structured to provide extended one-to-one contact between the educator and the diabetic. This contact allows the diabetic and the educator to develop a trusting relationship which becomes the context in which they work toward developing positive self-care attitudes.

The model ADEF program will be preceded by comprehensive training for the educators which includes inter-personal effectiveness training by a clinical psychologist in an systematic approach to influencing patient attitudes, as well as training in the teaching of knowledge and skills.

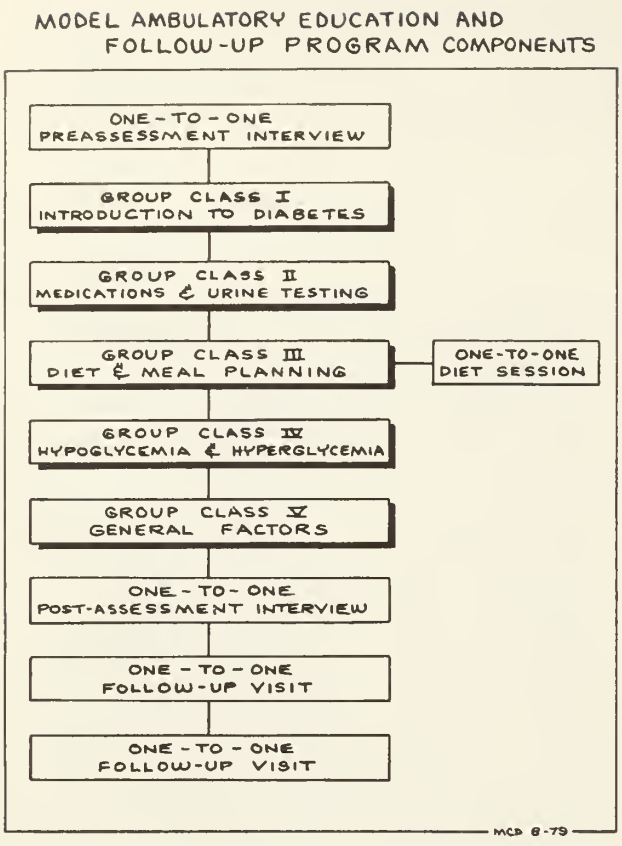
The model ADEF program is comprehensive in scope, educationally sound, and will be staffed by trained, committed educators. Thus, it has strong potential to add an effective component to the care received by diabetics in Maine.

II. Program Description

The initial phase of the model ADEF program, see Figure 1, will be an effort by program sponsors to work with local physicians to identify those diabetics and their family members who need diabetic education. Persons desiring to participate in the education program will be scheduled for an hour-long intake/preassessment interview with the nurse educator after being referred to the program by their physician. Hospitals and physicians will be encouraged to routinely refer their inpatients to the ambulatory program upon discharge from the hospital. During the preassessment interview, the nurse educator will do an indepth assessment of the diabetic's knowledge, skills, attitudes, learning style, medical history, and learning goals using specially designed instruments and procedures. This interview also allows the nurse educator and the diabetic to begin to form a trusting relationship. The nurse educator may then develop an educational plan based on individual needs.

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Figure 1



At the completion of this initial interview the diabetic and interested family members will be admitted to the next available program unit. The participant will attend up to ten hours of regularly scheduled comprehensive diabetic education. This classroom instruction will assist the diabetic in acquiring knowledge, developing skills, and adopting positive attitudes essential for good self-care. The diabetic and family members will also attend a one-to-one session with the dietitian to allow them to individualize the principles of good nutrition and diabetic exchange lists to their own meal plan.

Upon completion of the class work, the participant will be scheduled for a postassessment and referral interview. During the interview, the diabetic and nurse educator will select continued learning activities for the diabetic. At the end of the interview, the patient will be referred back to his/her physician who will be provided with full documentation of the education process. The nurse educator will contact the referring physician by telephone if more immediate communication is warranted. The written document for the physician will include classes attended, pre- and posttest scores, skills demonstration scores, educational referrals made, and comments and recommendations of program instructors.

Physicians will be encouraged to provide the education program with information on the patient's status, and refer the patient back to any portion of the program when needed.

Two follow-up visits by the patient to the nurse educator and/or dietitian will be scheduled within three months after completing the program for the purpose of reassessment and reinforcement of good self-care skills and attitudes. Documentation of these and other follow-up visits will be forwarded to the physician, and the patient will be instructed to stay in close contact with his/her physician. Also, patients will be encouraged to keep their appointments with physicians, nurses, dietitians, and other providers, as ordered.

At the end of one year the physician and his patient will each receive a letter from the model ADEF program requesting information about the patient's status; i.e., compliance control, or hospitalization, and also encouraging referral back to the program for reassessment and educational review, if warranted. The letter to the patients will advise them to see their physician if not seen on a regular basis. Unanswered letters will be followed-up by phone calls from the education program staff.

Diabetics confined to their home will continue to receive diabetic education through existing services such as home health agencies. Physicians may, however, refer a member of the home-confined diabetic's family to the ambulatory education program.

Allied health personnel such as home health nurses will be encouraged to attend the model ADEF program in order to provide consistent educational reinforcement to the diabetic.

The overall purpose of the model ADEF program is to supplement and reinforce the diabetic and his physician's efforts in achieving and maintaining successful management of diabetes and achieving a reduction of preventable morbidity and mortality.

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Diabetic Retinopathy

A Treatable Disease

William S. Holt, M.D., Kenneth P. Wolf, M.D. and Robert J. Takach, M.D.

Introduction

A hallmark of long standing diabetes is disease of the small blood vessels, affecting most vascular beds, and causing the functional and structural changes known as diabetic microangiopathy. Diabetic retinopathy is the term applied to this microangiopathy as it occurs in the retina. While the disability it produces is visual, it is nevertheless a vascular abnormality. It is a major cause of vision loss in the United States, possibly the leading cause of new blindness. The purpose of this paper is to review briefly what is known of the pathogenesis of diabetic retinopathy and to describe modern methods of treatment with the laser and with vitrectomy instruments. Over the past decade, the ability of ophthalmologists to treat diabetic retinopathy has improved greatly. For this reason, it is important that the medical community at large be aggressive in its recognition and referral of these patients. As was emphasized in an earlier review in this journal,[1] referral should result in more patients receiving more effective care with a consequent reduction in blindness.

The Magnitude of the Problem

In diabetics of juvenile onset, clinically detectable retinopathy is rarely seen at the time of diagnosis but by fifteen years after diagnosis, it is present in over 50%, and by twenty years in 75%. By contrast, retinopathy is already present in 25% of patients who are over forty at the time of initial diagnosis of diabetes, perhaps because adult onset diabetes frequently has been present for some time before its discovery. Twenty years after diagnosis, the incidence of diabetic retinopathy is 75% in this group also. A practical rule is that after ten or fifteen years of diabetes, patients of all ages have about a 50% chance of developing retinopathy, that is retinal changes readily detectable by the physician with the ophthalmoscope. These patients, of course, do not all have vision loss. Among patients with mild background retinopathy, about 80% will have visual acuity that is no worse after five years,[2] while about 20% will have poorer vision. Patients with proliferative retinopathy have a much worse prognosis, with more than 60% experiencing major vision loss in a five-year period.[2] In the population at large there is an annual incidence of new blindness of 1 per 10,000 from diabetic retinopathy.[3] Based on this, one would expect about 100 cases of new blindness from diabetes in Maine per year. This incidence is about twenty times that of blindness among non-diabetics from all other causes combined. It is clear that this is a major problem, both to the individual patient who has lost vision and from a public health viewpoint. Another aspect that must be considered is that diabetic retinopathy, being part of a generalized vascular disorder of blood vessels, is also associated with increased mortality. Patients with only microaneurysms have a survival rate as good as diabetics without retinopathy, but those with more severe retinopathy experience a significant mortality from renal and cardiovascular complications. The mortality rate among the diabetic blind, for example, is about 15% per year.[3]

Pathogenesis of Diabetic Retinopathy

Both clinically and in the laboratory the earliest detectable changes of diabetic retinopathy are an increased rate of flow and increased permeability of small blood vessels.[2] In patients with early diabetes and minimal retinopathy, angiographic studies indicate nearly double the blood flow seen in normal subjects. This increased flow may be an autoregulatory adaptation to the metabolic abnormality of diabetes, and in laboratory models, it is reversible with metabolic control, at least in its early stages.[4] Most diabetics, even those without clinically recognizable retinopathy, also show an increased leakage of serum from small retinal vessels when compared to non-diabetics.[5] Early microscopic findings are an increase in basement membrane thickness and a loss of both the mural pericytes which normally support the capillary endothelial elements and of the endothelial cells themselves.[6] As the retinopathy progresses, some capillaries become acellular and nonperfusing while others dilate and become shunt vessels or develop saccular microaneurysms. These changes create focal patches of retinal ischemia, infarcts ("soft exudate"), and leakage ("hard exudates"). It is not known what causes the capillary non-perfusion or indeed any of the early changes, but many theories exist relating them to metabolic[4] or rheological[5] factors.

Clinical Patterns of Diabetic Retinopathy

Once the pathological changes described above have developed, the retinopathy may take one of two alternative but not necessarily mutually exclusive clinical courses. In one type, predominant in "adult onset" diabetics, the dilated capillaries leak serum and lead to vision loss from macular edema and hard exudate formation or from ischemia. The second type, which occurs primarily in juvenile onset diabetics, is characterized by large areas of retinal ischemia and growth of abnormal new vessels. The first type is frequently referred to as "background retinopathy" and the second as "proliferative retinopathy", referring to the new vessels which

form.

Background retinopathy is the dominant pattern in adult onset diabetics. In most such patients the physician observes scattered microaneurysms, small hemorrhages, and occasional hard exudates. Only a very small proportion ever develop visual loss. Those who do may signal their impending problems by an increase in retinal ischemia or in the number of hard exudates. Hard exudates are accumulations of lipoprotein molecules which have leaked from incompetent vessels but are not reabsorbed. An increase in hard exudates or their assumption of a ring pattern ("circinate retinopathy") or an encroachment on the macula often is a precursor of macular edema and vision loss. Therefore, any increase in hard exudates is an indication for referral to an ophthalmologist who can arrange for angiography and possible laser treatment. Background retinopathy with macular edema usually leaves the peripheral visual fields intact, so these patients can perform many tasks of daily living even though they are unable to read or perform fine visual tasks.

Proliferative retinopathy is more characteristic of juvenile onset diabetes, although it is usually not seen until ten to twenty years after diagnosis of the diabetes. It is often asymptomatic until a retinal or vitreous hemorrhage occurs, but then it is associated with a very poor visual prognosis. With fluorescein angiography, large areas of retinal capillary nonperfusion are observed. Adjacent to these, or arising from the optic nerve, new blood vessels proliferate into ill-defined formations which tend to enlarge and grow along the retinal surface and into the vitreous gel. There is clinical and limited laboratory evidence suggesting that these new blood vessels may proliferate in response to a stimulating factor released by ischemic retinal tissue.[2] The new vessels have thin walls and a tendency to hemorrhage, often repeatedly, leading ultimately to opacification of the vitreous and a fibroproliferative retinopathy that may create traction retinal detachments. Although the prognosis of this type of retinopathy is poor, it is the type which is most amenable to treatment with the laser.

Another form of advanced diabetic eye disease is hemorrhagic glaucoma. Neovascularization of the iris and the filtration angle develops, obstructing aqueous outflow channels and leading to elevated intraocular pressure which is very difficult to treat. Rarely do these eyes retain good vision and present therapy is usually ineffective.

Role of Diabetic Control

Increased blood flow is the earliest detectable change in diabetic microangiopathy. In kidney and muscle, this flow increase is reversible with metabolic control of the diabetes,[4] althouth the reversal has not been demonstrated in the retina. Animal studies show that the retinopathy which develops in alloxan-diabetic dogs can be prevented or delayed by control with insulin.[7] The clinical data in humans, however, is not at all conclusive. The University Group Diabetes Program could find no difference in prevalence of diabetic retinopathy after nine to eleven years in subjects treated with diet alone compared with those on good control with insulin.[7] Results of other studies are similar, and at this time, there is no firm evidence that metabolic control has any influence upon the development of diabetic retinopathy in humans.

Evaluation and Treatment

Great advances have been made over the past fifteen years in the clinical evaluation of diabetic retinopathy. Retinal cameras are available which permit both color photography and angiography of the retinal circulation using sodium fluroescein as contrast medium. The technique has been nearly free of adverse reactions, so that angiography may be safely performed in either the hospital or office setting provided a physician and suitable emergency equipment are present. Fluorescein angiography gives precise delineation of the various components of diabetic retinopathy, especially points of abnormal vascular permeability and of new vessel formation. With the information provided by angiography, treatment with the laser can then be carried out. Angiographic and laser facilities are available at this time in Portland, Waterville, Lewiston, and Presque Isle.

Until the development of photocoagulation, the only measures which altered diabetic retinopathy were pituitary ablation and clofibrate. The former did have some beneficial effect but the endocrine consequences are so great that it is rarely performed and has very few indications at this time. Clofibrate may provide some clearing of hard exudates[8] but no visual benefits have been proven.

In background diabetic retinopathy, vision loss is due either to edema or ischemia in the macula. While photocoagulation obviously cannot reverse ischemia, several controlled studies have documented that eyes treated with the laser retain significantly better vision than control eyes.[8] Further, results were much better if treatment was performed before macular edema became firmly established. In other words, patients with background retinopathy who have significant exudate formation or retinal edema near the macular but who have not yet lost vision are those in whom argon laser treatment is most efficacious. Once edema has become established, treatment may lead to its clearing but the vision rarely improves due to irreversible degenerative changes. Early treatment is imperative if vision loss is to be prevented.

The beneficial effects of treatment of proliferative retinopathy have been well documented by the Diabetic Retinopathy Study Research Group.[9,10] Basically, laser treatment of eyes with neovascularization of the disc or retina with or without previous hemorrhage results in a significant regression of new vessels, a decrease in the frequency of major hemorrhages, and an overall 60% reduction in vision loss when compared to untreated control eyes in the same patient. The Diabetic Retinopathy Study

Research Group recommends that treatment of proliferative retinopathy by laser photocoagulation can be of definite benefit when the eye is most at risk, that is when disc new vessels are present. Treatment should be early, before new vessels have become massive or have hemorrhaged. The method of treatment is called pan-retinal photocoagulation and involves application of hundreds of laser burns to the peripheral retina. This retinal ablation appears to reduce the stimulus for new vessel growth, possibly by reducing oxygen need.[8] The therapeutic goal is regression of new vessel growth before major hemorrhage occurs.

In those patients with proliferative retinopathy in whom hemorrhage does occur, the vitreous gel immediately becomes cloudy with blood and vision is greatly reduced. While the vitreous may clear after one or two hemorrhages, after multiple hemorrhages it may become permanently opaque from old blood and secondary vitreoretinal membrane formation. The retina may become detached from traction as these membranes contract, causing loss of vision. A majority of these patients are in their middle years, so their blindness is particularly devastating. The blindness they suffer is total and complete, unlike that from macular edema. Vitrectomy is a new technique offering some hope to this group. In this procedure, a small probe with a cutting tip is used to remove opaque vitreous and membranes. The technique is difficult and requires complex instrumentation and should only be performed by surgeons who are also well versed in retinal detachment surgery. At this time, it is used only in eyes which have suffered major vision loss and while it is often dramatically successful in restoring vision, there are numerous and frequent major complications. There is a prospective study in progress by the Diabetic Retinopathy Study Research Group which should better define the indications and best timing for vitrectomy surgery.[11]

Suggestions for the Physician

In preparing this paper, we have tried to present the current status of our understanding of diabetic retinopathy and its treatment. Most ophthalmologists in Maine are familiar with recent advances and can advise when fluorescein angiography and/or laser treatment is advisable. It is recommended that all diabetics be referred to an ophthalmologist for a retinal examination at the time of diagnosis and regularly thereafter. Patients should be told that retinopathy is a possible complication and that good metabolic control may retard its onset. In juvenile onset diabetics, proliferative retinopathy is unusual before ten years of disease but may develop asymptomatically until a major hemorrhage occurs. Blindness can then be swift and complete. Therefore, these patients need ophthalmic referral if new vessels are noted on the disc or elsewhere and annual dilated retinal exams are certainly good practice. Adult onset diabetics tend to have background retinopathy for many years without vision loss. Referral is definitely indicated if a significant increase in hard exudates is noted or if visual acuity should become reduced. Annual ophthalmic exams are recommended.

Pregnant diabetic women are at particularly high risk of rapid and severe proliferative retinopathy. They must have careful retinal exams throughout pregnancy and after delivery. Laser treatment is indicated immediately if any progression of retinopathy is noted. These patients can progress to complete blindness with great rapidity and therefore serious consideration should be given as to the advisability of pregnancy in any patient with juvenile onset diabetes.

Patients who have become blind from diabetes should be registered with the Maine Department of Human Services, Bureau of Rehabilitation, Division of Eye Care, 32 Winthrop Street, Augusta, Maine 04330, using form REC-2674, available from that office. Numerous social services, such as homemaking aids, vocational training, talking books, etc. can be arranged through this department. The registration enables the Department of Human Services to keep accurate records of the number of diabetic blind.

In conclusion, over the past decade, diabetic retinopathy has become better understood and to a large degree is treatable. For this reason, aggressive referral of diabetic patients to ophthalmologists is advisable. Appropriate treatment can significantly reduce the incidence of blindness from this disease.

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Diabetic Neuropathy

Daniel H. Wood, M.D.

Introduction

Abnormality of nerve function in association with diabetes mellitus is common. Symptomatic polyneuropathy is present in 25% of diabetic patients, and electrophysiologic evidence of peripheral nerve dysfunction can be demonstrated in nearly all diabetic subjects.[1] In many patients, however, the symptoms are subtle and easily overlooked. The cause of diabetic neuropathy is not fully known and probably multifactorial. Its relationship to hyperglycemia and its improvement with "good control" of diabetes are still controversial, but a majority of diabetologists advise "good control" as a means of treatment and prevention of diabetic neuropathy. This position seems increasingly justified as more is learned about the metabolic factors that may contribute to nerve dysfunction. A review of the common symptoms of diabetic neuropathy together with some diagnostic aids and treatment suggestions will follow.

Nerve dysfunction can involve various anatomic segments of the peripheral nervous system. As a means of organization, it is useful to describe the neuropathies affecting these anatomic areas separately.

Radiculopathy—Dorsal nerve roots arise from the dorsal aspect of the spinal cord and contain nerve fibers carrying sensory input from the periphery. Diabetic radiculopathy is presumed to be caused by infarction within the sensory nerve roots due to thrombosis within the vaso nervorum—the blood supply of the larger nerves. It is relatively rate, and it presents as pain—ranging from a dull constant ache to intermittent sharp lancinating pain within the skin dermatome subserved by that root. A relatively subtle sensory loss can often be demonstrated in the same dermatome.

Mononeuropathy—The dorsal nerve root joins the ventral nerve root of the spinal cord to form a mixed spinal or cranial nerve which contains both motor and sensory fibers. These nerves may combine to form major nerve trunks such as the sciatic, the femoral, the ulnar, or the peroneal nerve. Infarction within one of these nerves causes a mononeuropathy, and when several such nerves are affected simultaneously, a mononeuropathy multiplex is produced.

Diabetic mononeuropathy can affect cranial nerves. Ophthalmoplegia due to involvement of the third, sixth, or rarely the fourth cranial nerves results in the sudden development of diplopia. Pupillary changes rarely accompany ophthalmoplegia. The onset of ophthalmoplegia is frequently preceded by several days of ipsilateral facial pain in the distribution of the trigeminal nerve. In this setting, the differential diagnosis includes tumors within the optic foramen or on the sphenoid ridge, pituitary tumors, myasthenia gravis, Grave's disease, and intracranial aneurysms. Since the risk of angiography is increased in diabetics, one must exercise especially careful judgment before its use. No treatment except eye patching is available for this condition, and resolution within several months can be expected with confidence. The association of diabetes with seventh nerve (Bell's palsy) and eighth nerve (auditory nerve deafness) dysfunction has not been clearly established but is frequently mentioned.

Diabetic mononeuropathies of the peripheral sensory nerves can mimic serious medical conditions such as coronary artery insufficiency, gallbladder disease, or an acute abdomen. EMG studies of the paraspinous muscles may be helpful when patients present with abdominal pain and diabetic neuropathy is suspected.[2] Motor involvement can be predominant in other instances resulting in characteristic paralyses such as foot drop. The onset of mononeuropathy is generally sudden and its distribution asymmetric. The pain associated with diabetic mononeuropathy may require narcotics for its control. Other forms of pain therapy will be discussed under diabetic polyneuropathy. In general, the prognosis in this condition is good with gradual resolution of the pain or paralysis within three to twenty-four months.

Polyneuropathy—Diabetic polyneuropathy involves nerve dysfunction of the distal portion of many nerves. It is characteristically symmetric and begins in the most distal aspect of the longest nerve. Instead of following individual nerve distributions, the sensory involvement is usually "glove and stocking." Diabetic polyneuropathy is insidious in onset and frequently not noticed by the patient. As mentioned in the introduction, perhaps 25% of all diabetics have some subjective symptoms of diabetic polyneuropathy, but virtually all diabetics have electrophysiologic evidence of impaired sensory nerve function. These symptoms range widely in quality and severity, and may be both motor and sensory although sensory involvement tends to predominate. The sensory manifestations include numbness, pins and needles, heaviness, aching, cramps, burning, and shooting pains. Characteristically this discomfort is most apparent at night, and unlike the pain of peripheral vascular ischemic disease, it is relieved by walking. There is usually a loss of sensation in the areas affected, initially vibratory and position sense. Not infrequently, however, there is hyperaesthsia resulting in a severe burning or pain sensation if this affected area is touched even by the slight pressure of clothing or sheets.

Motor loss, although less obvious clinically, is also a consequence of diabetic polyneuropathy. The loss of ankle jerks is convincing pathologic evidence of polyneuropathy. In the foot, muscle weakness as a

consequence of denervation leads to interosseous muscle wasting. Toe flexors, which usually balance the interosseous muscles, then predominate. This results in a "claw deformity" of the toes, and leads to abnormal pressure points and callus formation which further deforms the foot and misdirects pressure. This in combination with the loss of pain sensation results in neurotropic ulcers, most often on the plantar surface over the metatarsal phalangeal joints. These ulcers together with small vessel ischemic problems and infection lead to osteomylitis, potentially life-threatening infections, and amputation.

Another consequence of polyneuropathy is neuropathic arthropathy or Charcot's joint. This consists of bone lysis and fragmentation resulting from the lack of pain sensation and abnormal stress induced by inadequate proprioception. It results in painless swelling and deformity of the foot, flattened arches, and "rocker-bottom" feet. Because of the swelling it is frequently confused with congestive failure or venous insufficiency. X-ray studies show characteristic changes.

Although the lower extremities are most often involved by diabetic polyneuropathy, the upper extremities may also be affected. Painless cigarette and cooking burns occur. Muscle weakness of the hand can result in inability to perform simple work and household chores. It may also result in a wasting in the interosseous muscles along with the thenar and hypothenar eminences producing a characteristic appearance of the hands.

Accompanying these peripheral neuropatic changes is often a mental depression and irritability that leads to anorexia and insomnia. Although no specific central nervous system lesion has been described, the suspicion that CNS involvement accompanies peripheral neuropathy is supported by the frequent observation of elevated CSF protein in the 80-200mg/dl range. This finding is often used to support the diagnosis of polyneuropathy since other causes of peripheral neuropathy such as uremia, alcohol, and heavy metal intoxication, porphyria, or underlying carcinoma will not usually have increased CSF protein.

Polyneuropathy is probably not a consequence of arterial occulsive disease. At present it is felt to be a result of a metabolic imbalance induced in peripheral neural tissue as a result of diabetes mellitus. Glucose which is absorbed into neural tissue despite the absence of insulin is converted there to the alcohol sorbitol which is further metabolized into fructose. Neither of these molecules can pass freely outside the nerve cell. One hypothesis states that this results in osmotic swelling of the cells and damage.[3] Direct evidence to support this theory is as yet lacking and the site of damage—the supporting Schwann cell or the axon itself—has not been identified. More recent work has indicated myoinositol, a six carbon polyalcohol, is depleted in neural tissue of diabetic animals.[1] Glycosuria induces excess myoinositol loss.[4] This molecule is a constituent of phosphatidylinositol, a phospholipid involved in ionic flux that accompanies nerve impulse transmission. Depletion of myoinositol results in diminished nerve conduction velocity in diabetic animals.[1] A diet high in myoinositol has resulted in suggestive improvement in electrophysiologic nerve performance in man.[5,6] The consensus at present is that diabetic polyneuropathy is probably a multifactorial metabolic consequence of diabetes that effects the axon primarily with secondary Schwann cell changes.[1]

The course of polyneuropathy is slowly progressive. Although the pain of polyneuropathy may abate, this is due as much to further progression of nerve damage as to improvement. Improved control of hyperglycemias may be beneficial but there is little data to support this. In the control of pain, a variety of drugs have been tried. Dilantin® has been advocated although a recent double-blind study has shown it to be ineffective.[7] Carbamazepine in doses of 200mg qid in an uncontrolled study has been effective.[8] Combinations of the antidepressant amitriptyline and fluphenazine (Prolixin®) have also been effective in an uncontrolled study.[9] Transcutaneous nerve stimulation by means of a portable belt-worn pack inducing frequent small cutaneous shocks has helped.

Autonomic—The autonomic nervous system is another site of diabetic neuropathy. Although little is published concerning its causes, presumably it is metabolic and multifactorial as is the polyneuropathy. Symptoms depend upon the site of involvement.

Gastrointestinal—The esophagus is frequently found to be involved when examined by manometrics, but this rarely causes symptoms. Involvement of the stomach causes a loss of normal peristalis and delayed emptying—a condition known as gastroparesis diabeticorum. Symptoms consist of anorexia, fullness, nausea, and vomiting. Acid secretion may be diminished but is probably of little pathologic significance. The condition can generally be diagnosed by standard upper GI series. To date, the most successful treatment for the condition is metoclopramide, 10-15mg qid. This drug resembles procaine amide structurally, but is mechanism of action is not known.[10]* The experience with surgical approaches or parasympathomemetics has been discouraging.

Neuropathic involvement of the intestine can produce symptoms ranging from constipation to frequent watery diarrhea. Nocturnal fecal incontinence is a widely mentioned feature. Patients rarely exhibit features of malabsorption associated with diabetic neurotrophic enteropathy, but it has been described. Little effective therapy is available beyond the usual antidiarrheal agents. Pancreatic extracts are uneffec-

*Metoclopramide is not yet on the market in oral form. The A.H. Robins, Co., of Richmond, Virginia, has recently been allowed to place a parenteral form on the market. In an emergency situation, the A.H. Robins, Co. may be contacted.

tive and broad spectrum antibiotics or cholestyramine are rarely effective. Metoclopramide may be tried as a last ditch effort.

Autonomic neuropathy of the gut has a number of interesting implications with regard to diabetes and its control. Abnormal stomach emptying and gut motility may affect glucose absorption and insulin secretion. The release of gut hormones, which have both direct and indirect effects on insulin release, may be affected. Finally the autonomic nervous system may have direct effect on insulin release, and disturbance of this system may impair glucose hemeostasis.

Cardiovascular—Postural hypotension is the most clinically evident cardiovascular symptom. In effect, the heart is denervated, and the reflex tachycardia which ensues from the drop in effective plasma volume associated with the upright posture is lost. This, plus the loss of reflex arteriolar and venular constriction in the legs, leads to postural blood pressure drops which may exceed 30mm Hg and cause syncope. Whether this defect plays any role in the increased incidence of stroke or myocardial infarction in diabetics is unknown, but one study showed a 50% mortality over three years in patients with evidence of cardiovascular diabetic autonomic neuropathy.[11] The treatment for postural hypotension includes avoiding rapid positional change, especially after waking in the morning, sleeping with the head of the bed raised, support hose, and drug therapy. Florinef® in doses of 0.1-0.4mg daily can be effective.[12] Of course, one must watch out for excessive fluid retention, and patients with hypoalbuminemia can be especially sensitive to this effect.

Sweating—Loss of sympathetic tone in the lower extremities can lead to anhidrosis—lack of sweating. A more annoying accompanying feature of anhidrosis is hyperhidrosis in unaffected areas. Particularly in warm weather, patients complain of drenching sweats of the face, neck, and upper chest. Gustatory sweating, brought on by various foods especially cheese, alcohol, or vinegar, can also develop. Anticholinergics may be helpful in this condition.

Genitourinary—The bladder is a frequent and often overlooked site of diabetic autonomic neuropathy. Micturition is essentially a reflex of the detrusor muscle with voluntary control made possible by sensory input which signals fullness and by motor control of the external urethral sphincter. In a pathologic manner analagous to peripheral neuropathy, sensory loss and areflexia develops. The patient loses his sense of bladder fullness and the bladder dilates beyond its normal capacity of about 500cc. This increased capacity results in less frequent urination, an early symptom of bladder dysfunction. As the detrusor muscle weakens, it becomes more difficult for it to push down and open the urethral sphincters. This causes hesitency, straining, and a less forceful urinary stream. Overflow incontinence may occur. Generally the physician is unaware of this pathologic sequence until incomplete emptying results in a residual volume of urine greater than 50cc and infection ensues. These infections can be life threatening and when chronic can lead to deterioration of diabetic control. The abnormal bladder function leads to vesicoureteral reflux, hydronephrosis, and a chronic pyelonephritis. This insult added to preexisting diabetic nephropathy may lead to serious impairment of renal function.

Early treatment requires recognition of symptoms by the physician and can be as simple as encouraging urination every three to four hours. Ultrasonography may be useful in identifying excess residual volume,[13] and may be preferable to an IVP which produces increased morbidity in the diabetic. When a diabetic presents with a "suprapubic tumor" a week or ten days of drainage to allow the bladder to contract is required. After this frequent bladder emptying by suprapubic pressure, the Crede maneuver, or self catheterization should be instituted. Parasympathomentetic drugs, for example Bethanechol 10-30mg three to four times a day, may be added. If this fails to reduce the residual volume, surgery may be necessary. This consists of division of the internal urethral sphincter which is under involuntary control. In the male, this may be done by a transurethral resection. The result is a weakening of the urethral outlet in order to balance the already weakened detrusor muscle. Since the external sphincter which is under voluntary control is left intact, the patient will not become incontinent. Careful attention to diabetic bladder dysfunction can result in improvement of creatinine clearance if already impaired. The differential of this kind of bladder dysfunction includes benign prostatic hypertrophy, alcoholic neuropathy, vitamin B-12 deficiency, and spinal cord tumors.

Impotence afflicts as many as 30-60% of diabetic males. Erection is a parasympathetic function mediated via the pudental nerve. When this nerve is affected by diabetic neuropathy, erectile dysfunction results. Although psychologic factors must always be considered, several features help to differentiate this from autonomic neuropathy. Neuropathic impotence is generally gradual in onset, is not intermittent, is not associated with nocturnal erections, and is associated with a continued strong libido. In addition to history, a strain gauge designed to record nocturnal penile tumescense is commercially available and may help with the differential.

If the diagnosis is neuropathy, little therapy is available to reverse the process. Endocrine studies have not shown any hypothalamic, pituitary, or gonadal defect, so testosterone therapy would not be helpful. Silicone implants will help to restore function. Interestingly, female sexual dysfunction is not a well described consequence of diabetic autonomic neuropathy.

Retrograde ejaculation occurs when the internal urethral sphincter loses its competence secondary to neuropathy. As a result, the ejaculate flows into the bladder during ejaculation rather then forward through the penis. The only clinical problem with this

is infertility which can be treated by homologous artificial insemination of a centrifuged specimen of urine obtained after masturbation.

Conclusion

Diabetic neuropathy is a leading cause of morbidity in diabetes. Since its symptoms are often subtle and easily overlooked, a physician must be especially careful to detect its presence. Our understanding of the cause of diabetic neuropathy is limited, and our ability to prevent or reverse the underlying pathologic processes is questionable. Nevertheless, many of the symptoms of diabetic neuropathy can be treated effectively, and this will result in improved patient welfare.

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hospitalization (primary and secondary diagnosis), it is estimated that the total annual cost in 1975 for diabetic hospitalizations in Maine was $12.9 million. This averages out to a cost of $616 per year for every diabetic in Maine and does not include physician fees for hospital visits which could add another 14% or $85 per year. If costs continue to increase and in lieu of the development of intervention programs, by 1982 the cost of diabetic hospitalization may be as high as $35.3 million dollars, not including physician fees for hospital visits.[4]

Discussion

Studies[2,3,5] have shown that many of the problems of diabetics that require use of costly health services can be prevented with the development of a comprehensive program. Diabetes is a chronic disease problem of sufficient concern to justify a statewide approach to improve the overall health status of diabetics. The successful implementation of the Diabetes Control Project will result in the improvement of diabetic health status through reduced mortality and will reduce unnecessary utilization of costly health services.

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Juvenile-onset Diabetes

A Proposed Program

Joan MacCracken, M.D.*

Introduction

Juvenile diabetes mellitus is by far the most common pediatric endocrine disorder, affecting approximately one out of every 600 children. There are an estimated 80,000 school aged diabetics in the United States. Since the discovery and utilization of insulin, acute mortality from juvenile diabetes has been drastically reduced. However, it remains a chronic disease associated with the development of vascular complications involving the eye, kidney, and coronary and peripheral blood vessels.

Juvenile-onset diabetes varies significantly from maturity-onset diabetes. The onset of symptoms is more sudden and the need for insulin therapy is almost 100 percent. Management of the diabetic child or teenager is more difficult because of the life styles of children in general, including erratic dietary and exercise patterns and frequent emotional ups and downs. The physician must take into account these varying parameters to assist the parents and child in attempting to attain "good control."

Complications from diabetes are definitely related to the duration of the disease and more recently, scientific evidence seems to be confirming the important role of hyperglycemia in the development of these vascular changes. Thus, it seems that the challenge of juvenile diabetic management is to maintain normoglycemia ("good control") as best as possible *while* allowing the child or teenager to participate as normally as possible in his environment.

Continuing education and update for the parents and diabetic child should be a large part of the medical management. With a solid understanding of current diabetic management and with the hope of improved therapeutic modalities, such as continuous infusion pumps or pancreatic transplants, family and patient should be well equipped to carry on the treatment program.

Diabetes in Maine: A Proposed Program

As of 1974, in Maine, there were 111 new cases of diabetes under age 17 diagnosed annually. At this time, there are no programs available in the state of Maine for following juvenile diabetes in a specialized outpatient clinic. The closest facility providing a comprehensive team approach is in Boston. It is unrealistic to have Boston be the treatment and educating center for all Maine diabetics and for physicians who wish to keep up to date.

The goal of such a juvenile diabetic clinic would be to improve overall patient care by:

1. Monitoring diabetic control with the latest laboratory methods. Currently 24-hour block urines for glucose determinations and glycosylated hemoglobin levels could be used.
2. Providing an educational environment to expose the parents and patient to the latest information on diabetes—its causes, its management and its future.
3. Giving psychological support to family and child, including offering a meeting place for both parents and diabetic children who so often feel quite isolated and alone.
4. Centralizing and recording other medical follow-up such as ophthalmologic examinations, and nutritional guidance and review.
5. Providing genetic counseling services including possible HLA typing.
6. Shortening the initial hospital stay by providing a less expensive, yet more advantageous outpatient service.
7. Decreasing the need for hospitalization due to poor follow-up and management.
8. Offering ongoing education to the general physicians who are caring for these patients on a day-to-day basis including visits by professors from renowned diabetic centers.

By providing these services, a significant contribution could be made toward decreasing morbidity and mortality of juvenile diabetics and improving the general health and outlook of the diabetic children here in Maine.

The future plan is to establish such a clinic at the Eastern Maine Medical Center.

Summary

Juvenile diabetes mellitus is the most common endocrine disorder in childhood. Management of the juvenile diabetic can be frustrating and complex. An organized approach of follow-up and education is necessary. Currently in Maine there is no specialized ambulatory clinic for the juvenile diabetic. Such a clinic could offer many advantages to these patients.

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Gestational Diabetes

Diagnosis and Treatment

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ABSTRACT

It would appear that Maine has statistically lower *reported* gestational diabetes rates than other states (1.2% for Maine vs. 2.3% of pregnancies as reported by the National Commission on Diabetes). This preliminary report would lead the clinician to ask whether gestational diabetes is indeed lower in Maine or whether this represents a failure in screening, recognition, or reporting. Only continued statistical analysis will resolve this question. It is the purpose of this paper to present a working protocol which is statistically precise and cost-effective for the clinician and his patients.

After reviewing the medical literature on gestational diabetes, it becomes clear that the final word in the research, diagnosis and treatment of this altered carbohydrate metabolic state has yet to be published. There are, however, generally accepted guidelines to help the clinician in the diagnosis and treatment of this disorder.

In order to provide optimum therapy, the physician must have a substantial understanding of the physiology of normal pregnancy as it pertains to carbohydrate metabolism. Pregnancy itself is a diabetogenic state which in a certain percentage of patients will result in increased insulin resistance and hyperglycemia beyond the normal physiologic range of glucose homeostasis. Maternal age, obesity, placental hormones and enzymes all play a role in carbohydrate metabolism which are only mentioned here because detailed discussion of them is beyond the scope and intent of this paper. The goal of establishing treatment of gestational diabetes is to reduce perinatal morbidity and mortality. More specifically, it is our desire to eliminate fetal macrosomia, neonatal hypoglycemia, neurological and bone morbidity due to shoulder dystocia, reduced cerebral development, and fetal compromise at term.

Gestational diabetes is defined as those pregnancies with 2 abnormal blood glucose values on a standard oral 100 gram 3 hour GTT, excluding known overt diabetics, newly diagnosed diabetics (abnormal GTT, classic diabetic symptoms, and/or blood glucose greater than 300mg%).[5] It is a state of abnormal maternal carbohydrate metabolism beginning at any stage of gestation and totally absent by the 6th post partum week. Gestational diabetes is found 3 times more frequently with multiparous pregnancies than with primiparas. Increased perinatal loss appears to exist in the 25 year old patients or older. Seventy-nine percent of gestational diabetics are detected by a single blood sugar 1 hour after a 50 gram glucose load. Eighty-eight percent are detected with this same screen in pregnant women of 25 years or older.[5] The treated group of gestational diabetics have a perinatal mortality less than or equal to 1% whereas the untreated group result in a 6% perinatal mortality. Perinatal morbidity is reported by one author at 8% (½ of which was due to or related to birth trauma secondary to fetal macrosomia).[6] Fetal macrosomia is defined as fetal weight equal to or greater than 8½ pounds/4000 grams. With treatment of gestational diabetes, the incidence of fetal macrosomia can be reduced to the following: insulin and diet = 7%, diet alone = 36.4% and no treatment = 50%.

The following protocol is suggested as an acceptable mode of diagnosis and treatment of gestational diabetes.

PHASE I — DIAGNOSIS

STEP #1 — History risk factors:

1. Previous poor obstetrical result
   a. Unexplained fetal demise.
   b. Habitual aborter.
2. Birth of a large neonate (greater than or equal to 8½ lbs./4000 grams).
3. Maternal obesity (greater than or equal to nonpregnancy weight 20% over ideal).
4. Maternal age (greater than or equal to 25 years).
5. Glycosuria.
6. Family history of diabetes especially with a primary relative, father or mother.
7. Presence of polihydramnios.

STEP #2—

A. All non-risk pregnant gravidas should have a 1 hour serum glucose determination after ingestion of 50 mgs. of glucose as a minimum screen. (Normal = less than or equal to 130 mg%).

B. If any one or more of the above factors (step #1) are positive, a 3 hour GTT should be performed as the initial screen.

C. If step 2A is greater than 130 mg%, a standard 100 gram oral 3 hour GTT is performed.

NORMAL VALUES

	Somogyi-Nelson method	*Hexokinase method*
Fasting	90 mg/100 ml	100 mg/100 ml
1 hour	165 mg/100 ml	180 mg/100 ml
2 hour	145 mg/100 ml	160 mg/100 ml
3 hour	125 mg/100 ml	140 mg/100 ml

Gestational diabetes is diagnosed when 2 or more of the above values are met or exceeded.

STEP #3—

If steps 2B or 2C are negative, the 3 hour GTT is

repeated at 28 weeks' and 36 weeks' gestation.

STEP #4—

If steps 2B, 2C, or step 3 are positive, the patient should undergo appropriate treatment for gestational diabetes.

Phase II — Treatment

STEP #5—(Prenatal)

All gestational diabetics should be placed on a total caloric diet calculated from (.9 Cal/kgm. body weight/hour times 24 plus 300 calories) with a 30% increase for light activity, 50% increase for moderate activity and 75% increase for heavy activity. The distribution of the diet should be 50% carbohydrate, 20% protein, and 30% fat. (Approximates: 200 gram—carbohydrate; 100 gram protein; remainder fat). The diet should be increased in 200 calories a day increments with the appearance of starvation ketonuria. In the severely obese patient, a decrease of 200 calories a day increments can be achieved provided starvation ketosis is not reached and weight gain is maintained at a minimum of .25 lbs. per week.

STEP #6—

If dietary treatment alone does not achieve baseline blood glucose levels below 100 mg% (tested on 2 separate occasions), insulin therapy should be initiated. Ten units NPH in A.M. is a good starting point but one may have to modify the dose and regimen based on a serum glucose screen tested throughout the day (this author prefers FBS, 2 hour PPBS, 4:00 P.M. BS, and 10:00 P.M. BS). The goal is to keep baseline serum glucose levels below 100 mg%, and postprandial levels within 2 standard durations of the normal.

STEP #7—

100 mg. of vitamin B6 per day may be helpful in improving glucose tolerance with a lowering of blood glucose levels at all points of a GTT. (Relative deficiencies in B6 have been associated with gestational diabetes. Low vitamin B6 appears to alter metabolic pathways which results in a lowering of the biologic activity of endogenous insulin).[3]

STEP #8—

Selection of Time to Terminate Gestation (37-40 weeks)

A. It is generally felt that most gestational diabetics can deliver spontaneously provided this is not contraindicated by:
   - #1. Fetal size greater than or equal to 4000 grams.
   - #2. Abnormal FAD and/or OCT.
   - #3. Low normal or dropping estriols.
   - #4. Other pregnancy complications; if early delivery is anticipated, amniocentesis for L/S and PG determination may be helpful.

B. Weekly 24 hour urinary estriols should be collected from 28 weeks in the gestation. FAD and/or OCT may also be performed on a weekly basis to evaluate fetal well-being.

STEP #9—Intrapartum and Postpartum Treatment

A. Insulin is withheld on the day of parturition.

B. Fifty grams of glucose is given as a 5% D/W solution during a 6-hour period.

C. During the first 24 hours postpartum insulin requirements are usually markedly decreased; consequently, careful monitoring of both glucose and insulin needs of the patient are maintained.

D. The patient's nonpregnant metabolic state may not return to baseline before the 4th or 6th week postpartum.[1]

STEP #10—

Three hour GTT at 6 weeks to insure that normal carbohydrate metabolism has returned.

Addendum

Infection, ketoacidosis, preeclampsia, polihydramnios, fetal distress, IUGR, may require hospitalization of the diabetic patient.

Summary

There does seem to be a concensus in the medical literature that diagnosis and treatment of class A, gestational diabetes, results in lowered perinatal morbidity and mortality and may also have long-term benefits for maternal health.

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Unstable Diabetes

A Review of the Causes and Some Suggestions for Management

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Introduction

It is well known that there is a relatively small percentage of diabetics who, in spite of reasonable control measures and patient compliance, exhibit wide, unpredictable fluctuations in blood sugar levels. These patients are usually ketosis-prone as well. They are variably referred to as "brittle," "labile" or "unstable." They are all of the insulin dependent or "juvenile" type of diabetes. Management is often difficult and frustrating to all concerned. Often, the patient is branded, unjustly, as uncooperative. While there is no simple solution to this problem with our currently available tools, an understanding by both physician and patient of the mechanisms involved in lability may improve management considerably, reduce hospital admissions and generally improve "quality of life." The effect of better control on long-term complications remains speculative, but there is a growing consensus among diabetalogists that hyperglycemia is a major factor in production of microvascular and neuropathic problems. Research developments over the past decade have contributed much to an understanding of unstable diabetes. These include constant glucose monitoring, the radio-immunoassay techniques with determination of the blood levels of insulin and the various hormones involved, and more recently the C-peptide assay.

Factors Effecting Glucose Homeostosis

Insulin is the major regulator of the blood sugar. The normal Beta Cell responds rapidly to even small changes in blood sugar levels by increasing or decreasing insulin output. Minute-to-minute control of blood sugar within a fairly narrow range is normally achieved largely by the effect of insulin on hepatic glucose output. Insulin further controls the blood sugar on a slower basis by regulating the amount of amino acids available to the liver for gluconeogenesis. The degree to which insulin effect is impaired correlates closely with the degree of stability in a diabetic.

Glucagon transiently increases hepatic glucose output, thereby raising blood sugar. Glucagon is released in response to a variety of stimuli, particularly hypoglycemia. In the diabetic, glucagon secretion may be inappropriate or blunted in which case one of the protective mechanisms against hypoglycemia is lost. A recent article describes circulating antibodies to glucagon in diabetics and it was felt that the diabetics with these antibodies were more hypoglycemia prone.[1] In experimental animals, it is found that ketoacidosis occurs much less readily in the absence of glucagon. In animals and humans, the "Stress Hormones" (Cortisol, Catechol amines, Growth Hormone, and glucagon) are found to be important in the production of ketoacidosis in the insulinopenic patient.[2]

Catechol amines not only raise blood sugar by stimulating hepatic glycogenolysis, but also stimulate lipolysis and are therefore ketogenic as well. The clinical significance of this is that emotional upset can produce significant elevation of blood sugar and even ketoacidosis in the diabetic. In practice, emotional factors are often overlooked as a cause of problems with diabetic control.

Corticosteroids and *growth hormone* are diabetogenic but generally produce stable elevation of blood sugar. The absence of these hormones as in pan hypopituitarism or Addison's Disease may result in marked insulin sensitivity and problems with severe hypoglycemia in the insulin taking patient. *Thyroid hormone* does not have a direct role in the regulation of blood sugar, but the presence of thyrotoxicosis will cause worsening of the diabetic state. Myxedema may result in increased sensitivity to insulin.

Insulin antibodies and insulin binding as well as antibodies against insulin receptors on the cell are mentioned in passing as they obviously effect the diabetic state but are not usually a major factor in unstable diabetes.

Information Derived From Newer Techniques

Constant glucose monitoring over a 24-hour period in insulin dependent diabetics has been very illuminating.[3] In the unstable diabetic, even when seemingly fairly well controlled, frequent fluctuations of blood sugar from 30 to 300 mg.% may be demonstrated. It becomes apparent that a random or single timed blood sugar in this type of patient is of little value. One of the most important things learned, however, was that the dips into the hypoglycemic range were frequently not symptomatic. These unrecognized hypoglycemic periods trigger release of catechol amines and glucagon with a rebound hyperglycemia, often referred to as the "Somogyi effect." These patients spill sugar, and even ketones during the rebound and may mistakenly be thought to need more insulin when in fact they may need a considerable reduction of insulin dosage.

The C-peptide assay,[4] by serving as an indicator of endogenous insulin production, has shown that the sine qua non of the unstable diabetic is that these diabetics produce little or no endogenous insulin.[5,6] Insulin is produced by the Beta Cell initially as a larger, inactive, molecule called Pro-insulin. A portion of this molecule is split off leaving the well

known active two-chain insulin molecule and a biologically inactive polypeptide called the connecting or C-peptide. Therefore, for every molecule of insulin produced there is a C-peptide molecule released as well. An assay of C-peptide, then, corresponds directly to the amount of endogenous insulin produced, circumventing the problems of attempting to measure insulin levels in insulin-taking diabetics who all develop varying amounts of insulin antibodies which interfere with the insulin assay. A second advantage is that while insulin is partially removed from the Splanchnic circulation by the liver, C- peptide is not. Hence, a peripheral blood value of C-peptide accurately reflects the amount of insulin released from the pancreas.

It had been thought that insulin dependent diabetics lost their ability to produce any insulin within a few years of the onset of their diabetes. Studies using the C-peptide assay have shown that some diabetics produce insulin for as long as 20 or more years.[7] If a diabetic can produce some insulin on demand, albeit much less than necessary, it can serve as a stabilizing factor. In this type of diabetic, if not enough exogenous insulin is given, the endogenous production can supplement it. If a little too much insulin is taken, the Beta Cell can turn off, decreasing the total amount of insulin and acting as a buffer against hypoglycemia. These patients who produce some insulin tend to be the stable type who may get along well with a single daily dose of NPH or Lente insulin, and are less ketosis prone while a patient totally dependent on exogenous insulin becomes unstable and ketosis prone, usually requiring split NPH or Lente doses and usually added regular insulin as well.

Management Suggestions

General

Probably the first thing both physician and patient have to learn is that it is not going to be possible to set up a constant dietary and insulin regimen. Both diet and insulin may have to be changed intelligently in relation to amount of physical activity, emotional stress, illness, etc. The only person who can do this well is the patient. This implies a high level of diabetic education and motivation. Diabetes, particularly insulin dependent, is a "do it yourself" disease, with the physician's role that of an advisor, teacher, and treater of complications. Furthermore, in unstable diabetes, one cannot afford the luxury of a laissez-faire or loose control approach, because regardless of one's philosophy about long-term complications, short-term problems of hypoglycemia and ketoacidosis will occur unless there is reasonable structure and attention to detail in the program.

Insulin

As alluded to above, these patients do better on split doses of an intermediate acting insulin (NPH or Lente) with added regular insulin to one or both of the a.m. and p.m. doses. Once a reasonable level of intermediate acting insulin is reached, it is probably best not to make frequent changes in this, but change the amount of regular, plus added increments of regular to compensate for excess glucosuria and ketonuria. This is where the properly educated patient can learn his own changing needs and often make a better judgment than the professional. Over insulinization with rebound hyperglycemia is to be watched for and avoided. Another effect of over insulinization is to make an unstable out of a stable diabetic by suppressing endogenous insulin secretion and depriving him of the regulatory effect his own insulin may have.

Diet

For the non-obese diabetic, diet can be quite flexible in the sense that types and amounts of foods and snacks can all be tailored to the individual needs and likes, but once planned, the diet must be fairly rigid in terms of timing of feedings and amounts at each meal, an exception being adjustments the patient makes rationally to accommodate changes in activity. Mention should be made of recent work with increased fiber diets in diabetics with the indication that fiber slows glucose absorption and blunts postprandial blood sugar peaks.[8,9,10]

Monitoring Control

Occasional office blood sugars are probably of little value in evaluating control in the unstable diabetic. In the absence of seriously altered renal threshold for glucose, urine testing of one type or another on a regular basis, nuisance that it is, is still the most practical method of assessing control and making adjustments in the diabetic program as well as forestalling acute complications.

Home monitoring of finger stick blood sugars using Dextrostix® is coming into increasing use.[11] Crude but useful values may be obtained from a simple color chart. More accurate values are obtained using a photometric method for reading the Dextrostix such as the Ames Eyetone® machine. Unfortunately, the cost of this machine is approximately $400.00. Its use should probably be limited to situations where frequent, relatively accurate home blood sugars are necessary, unstable diabetes being one indication.

Glycosolated (A_{1c}) hemoglobin may be of some help in overall assessment of degree of control over a period of weeks, but will not pin point where and how the program needs to be changed.

Criteria for Control

More and more evidence is being produced, with increasing physician acceptance, that at least the microvascular and probably the neuropathic complications of diabetes are related to hyperglycemia. Consequently, an effort should be made to educate, motivate, and control every diabetic as well as possible.

It is suggested, arbitrarily, that good control implies fasting and three-hour p.c. blood sugars less than 120 mgs. %. In mild diabetics this is readily

achieved with good patient compliance. In the unstable diabetic this is much more difficult, but the goal should be the same even if in some patients the best we can do is to keep them asymptomatic. In the diabetic pregnancy where blood sugar control is generally accepted as very important to the outcome and patients are particularly well motivated, close control is often possible, implying that similar control could be achieved in other diabetics with the same motivation and effort.

Summary

Unstable diabetes may be due to a variety of factors, but the principal cause is the lack of ability of the individual to produce any significant amount of endogenous insulin. Suggestions for management are offered, one of the most important being that of educating and motivating the patient to understand his disease and to make appropriate adjustments in his program whenever indicated.

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Developing a Diabetes Control Project in Maine—*Continued from Page 6*

continuing education for health care professionals. In the past year diabetes-specific programs were presented for nurses, dietitians, and physicians in three regions of the State. These efforts will continue during the next year with increased emphasis on programs for physicians which focus on the role of patient education in the management of their diabetic patients.

The fourth area is the coordination and linkage of inpatient education with ambulatory or outpatient educational programs to assure effective use of teaching manpower and the most effective educational setting for the diabetic.

The fifth and final area is to develop guidelines for identification and modern management of diabetic pregnancies. (See articles on pages 17 and 22.)

Successful development of a Statewide diabetes health care system will require the cooperation, commitment, and participation of all segments of Maine's health care resources, and will result in improvement of the overall health status of the Maine diabetic.

Management of the Pregnant Diabetic: 1979

David L. B. Eldredge, M.D.*

With the advent of insulin in the 1920s, the female juvenile onset diabetic began to survive well into adulthood. As diabetic control became more sophisticated, fertility improved and diabetic women began to carry babies toward term. With diabetic pregnancies came a whole new spectrum of problems for the obstetrician and diabetologist. Management of these pregnancies evolved. Some therapies, such as DES, have been discarded, while other aspects of management have been modified and improved. This review will discuss the current methods of management of the diabetic pregnancy today, with special emphasis on our own experience at Maine Medical Center.

During the prenatal period the obstetrician must look for diabetes. Diabetes is seen in 1-2% of all pregnancies.[6] The women at risk tend to be; the obese patient, the patient with a family history of diabetes, and those women with a previous large baby (over 4,000 grams), a malformed baby, or previous unexplained stillbirth. These women should have at least a fasting blood sugar and two hour post-prandial blood sugar at their initial evaluation in the first trimester, and then again in the third trimester. Although glycosuria can be physiologic during pregnancy because of increased GFR, any patient with glycosuria should be evaluated for diabetes.

The fasting and two hour post-prandial sugars provide a screening test for diabetes. If these sugars are suspicious (greater than 120 mg.% whole blood or greater than 140 mg.% serum at 2 hours), or if the obstetrician still suspects diabetes, then a three hour glucose tolerance test should be performed. Because the carbohydrate metabolism of pregnancy differs from that of the non-gravid state, different standards apply to the GTT. Normally, the fasting whole blood glucose is 55-65 mg.% in the non-diabetic gravid patient. Conversely her response to a glucose challenge is blunted by insulin antagonists such as HCG, HPL, estrogen, progesterone and cortisol. The GTT most widely accepted for diagnosis of the pregnant diabetic is that of O'Sullivan and Mahon[22] (See Table 1).

If the GTT is abnormal, but the fasting blood sugar remains normal, the patient is a Class A diabetic. These women by definition do not require insulin and can be controlled by diet. Some workers have recently suggested that giving token doses of insulin (e.g., 10 units NPH daily) can prevent macrosomia and placental hypertrophy in Class A diabetics.[23] Early data suggest that this is true and are consistent with our current concepts of macrosomia and diabetes, but this has not yet entered the mainstream of diabetic care.

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Table 1

Glucose Tolerance Test

Time	*Blood Glucose*	
	Pregnant	*Non-pregnant*
Fasting	90	110
1 hour	165	170
2 hours	145	120
3 hours	125	110

The Class A diabetic generally enjoys a normal pre-natal period and is spared the expense and bother of the management protocol which will follow in this review. Her diet should have no concentrated sweets and should average 2200 calories per day so that she will remain in an anabolic state. She should be seen about every two weeks looking for ketonuria, or increased glycosuria, heralding worsening of the diabetic state. If ketonuria develops, then the diet must be increased. Careful attention should be given to establishing obstetrical dates by landmarks and sonograms. The Class A diabetic can be allowed to go to term as in any normal pregnancy. However, if she goes past 40 weeks, she then becomes a high risk patient and requires increased surveillance. Delivery of the infant requires careful obstetrical judgement. If the estimated fetal weight is 4,000 grams or more, there is a 3.8% incidence of shoulder dystocia. If the fetal weight is 4,500 grams or more, the incidence of shoulder dystocia is 13.6%.[12] If there is any doubt about the adequacy of the pelvis for an infant over 4,000 grams, then Caesarian section should be performed. Once in the nursery the infant of the Class A diabetic must be observed for hypoglycemia and hyperbilirubinemia.

The Class B through R diabetics pose a more difficult management problem. These patients and their infants face greater dangers if not managed properly.

Prenatal management really begins prior to pregnancy. If the patient is a known diabetic, the pregnancy must be planned after the patient's diabetes has already been in good control. If the known diabetic desires pregnancy or if a pregnant patient is discovered to have diabetes, careful counseling of the potential parents must be undertaken by the physician. The risks to the fetus must be carefully outlined. The infant of the diabetic mother has a 1 to 5% chance of becoming a diabetic as well.[19] The fetus has a 3 to 5% chance of dying in the perinatal or neonatal period.[7] Of these deaths, 40% will be due to congenital malformations.[19] The overall incidence of malformations in diabetic pregnancies is 11%,[16] with 7% incidence for classes A, B, and C and 22% incidence for classes D and F. The most common malformations are cardiac and skeletal (about 35%

incidence for each).[16] The chances of a third trimester intrauterine death, respiratory distress syndrome in the newborn and fetal macrosomia with consequent chances of birth trauma must be discussed in full. At the same time, a strong case for diabetic control must be made. Numerous studies have indicated that strict control of diabetes may prevent many of these complications. Pederson has shown a strong correlation between high blood sugars in the first trimester and congenital malformations.[19] This has also been found in another clinical study by Karlsson and Kjellmer[15] and in an animal study by Horie.[14] There is some evidence that fetal hyperinsulinemia from a high maternal glucose can inhibit surfactant production in the fetal lung. A strong theoretical case can be made for good control preventing intrauterine fetal death. Many years ago, Pederson proposed that macrosomia was related to maternal hyperglycemia and fetal hyperinsulinemia. Some cases have supported this theory.[27,19,6,7] However, Karlsson and Kjellmer were unable to show this correlation of hyperglycemia with macrosomia,[16] although overall perinatal mortality dropped considerably with good diabetic control. The bulk of data thus strongly advocates strict control of glucose in improving perinatal outcome.

The diabetic must also be warned that a diabetic pregnancy can be costly in several ways. The diabetic mother may require several hospitalizations during her pregnancy for diabetic control and complications. She must realize that she may require several weeks of hospitalization at the end of her pregnancy, and then the infant may require prolonged hospitalization following birth in a neonatal I.C.U. The monetary expense can be staggering, as well as a marked disruption of her family life. Also, depending on the severity of the diabetes, the long term maternal prognosis may be poor. There is conflicting data on whether pregnancy adversely affects the vascular degeneration of diabetes. However, a Joslin Clinic study of mothers from 1924-1970 showed that one out of five children of diabetic mothers had lost their mother by their tenth birthday.[19]

Armed with this knowledge, if the couple decides to continue the pregnancy, most diabetics and their families then make a strong effort at strict diabetic control.

Over the last few years, marked changes have taken place in the dietary and insulin management of diabetic pregnancies. As recently as 1974, Priscilla White insisted on a weight gain of only 12 pounds and limiting the diet to 30 calories per kilogram of the ideal body weight (1500-1800 calorie per day diet).[26] This stance has been refuted by several studies and now the recommendation is that the pregnant woman gain 25 to 27 pounds and that she have at least 38 calories per kilogram of actual weight.[19] In other words, the average pregnant woman should have a diet of about 2200 calories, with 200-250 grams carbohydrate, at least 70 grams of protein* and about 100 grams of fat.[19,1] This is usually divided into three meals (630 calories each) and an evening snack (310 calories),[1] although six smaller meals a day are sometimes required. Pregnancy is no time for weight reduction and ketosis must be avoided at all costs. Ketosis has been demonstrated to result in poor perinatal outcome and lower I.Q. scores in the children.[2] If ketones appear in the urine and blood sugar is reasonably controlled, then more carbohydrate must be added to the diet.

Insulin therapy becomes more complicated as the pregnancy progresses. Initially, the insulin requirement may fall in the first trimester but it then increases during the second and third trimesters to about 166% of the pre-pregnancy insulin requirement.[26] The main cause for this rise in insulin requirement appears to be human placental lactogen, a growth hormone-like substance, and enzymes in the placenta which degrade insulin. Increased maternal cortisol, estrogens and progesterone probably also play a role. It is consistent, then, that diabetics with severe vascular disease who tend to have smaller placentas also tend to have a smaller rise in insulin requirement (156% of pre-pregnancy dose).[26] Likewise, when the placental unit is malfunctioning, as when the fetus is in jeopardy or already dead, the insulin requirement suddenly drops. And following the delivery of the placenta, the insulin requirement is dramatically lower than the pre-pregnancy dose for several days until the mother's anterior pituitary begins to secrete growth hormone again.

Although it is now well agreed that ketosis is bad for the fetus, controversy remains over what blood glucose level is optimal control of the diabetic mother. Most obstetricians at the Maine Medical Center now feel that tight control is desirable. This is based on the knowledge that the normal pregnant woman has a fasting blood glucose of about 65 mg.% and rarely has a blood glucose above 100 mg.%.[19] It is also based on a retrospective study by Karlsson and Kjellmer who found that in 179 diabetic pregnancies over a ten year period, perinatal mortality was 23.6% if the mean blood sugar was above 150 mg.%. It dropped to 15.3% if the mean blood sugar ranged between 100-150 mg.% and then dropped to 3.8% if the blood glucose was under 100 mg.%.[16] On the other hand, insulin reactions have not been found to be a danger to the fetus. Transient drops in blood glucose below 50 mg.% do not appear to hurt the fetus, however, in our experience a prolonged glucose of about 50 mg.% over several hours resulted in an infant who had idiopathic seizures in the nursery for a 24 hour period.

Oral hypoglycemic agents have no place in the management of the pregnant diabetic as these agents may cross the placenta. Insulin, which will not cross the placenta, is the drug of choice. Numerous reviews on the subject give various cookbook insulin regimens for controlling the blood sugar. Any regimen

*Some authors recommend up to 125 grams of protein per day.

which will keep the blood sugar close to 65 mg.% to 100 mg.% is acceptable. If the obstetrician does not feel comfortable with insulin, then an internist may be recruited provided that he is motivated to tightly control the blood sugar. At Maine Medical Center, we generally use split dose NPH and regular insulin in the morning (⅔ of total dose) and in the early evening (⅓ total dose) which is then adjusted to the individual needs of the patient. While hospitalized, we generally get blood sugars two to four times a day. We rely on twice daily blood sugars, once or twice a week, to manage the outpatient. Some private offices have started using Dextrostix® and have the patient check blood glucose at home. This has been fairly successful and may become standard management in the future.

During the course of the pregnancy, the gravid diabetic and her fetus are particularly vulnerable to several complications. The progression of vascular disease is variable. Retinopathy may progress to a proliferative stage, so careful examinations of the fundi must be done during pregnancy. Women with coronary disease are particularly vulnerable because of the cardiac stresses of pregnancy and can have a high mortality from myocardial infarction.[19] Nephropathy of diabetes does not seem to be altered by pregnancy, but urinary tract infections are higher in the pregnant diabetic,[26] and these infections are associated with premature labor and cerebral defects in the fetus.[19] As pregnancy advances the mother becomes more prone to ketoacidosis and, as noted, ketones are associated with higher fetal mortality and morbidity. If coma from diabetic ketoacidosis occurs (CO_2 less than 10 mEg), the fetal loss approaches 90%.[26]

Several obstetrical complications are more common in the diabetic mother. Hydramnios occurs in roughtly 25% of diabetic pregnancies and may lead to premature rupture of membranes and/or premature labor. Although pre-eclampsia was common in diabetics forty years ago, it does not appear to be greatly increased over the general population today. Intra-uterine growth retardation is common in white classes D through R while macrosomia is the rule in classes A, B and C. The greatest obstetrical complication is sudden intra-uterine fetal demise and is most common after the 36th week.

The attempt to prevent this sudden intra-uterine death syndrome has resulted in routine admission at 34 to 36 weeks gestation and the performance of multiple tests to assess fetal well being. We generally admit the patient by 36 weeks at Maine Medical Center, but recently some patients have succeeded in later admission by careful monitoring of blood sugar, estriols, and fetal activity determinations as outpatients. Other centers are doing likewise.

Our usual repertoire of tests consists of serum unconjugated estriols, fetal activity determinations (non-stress tests), and periodic amniocentesis for LS ratio and phosphatidylglycerol. We are currently trying to assess their cost/benefit ratios and their role in making obstetric decisions.

Serum unconjugated estriols are generally obtained at weekly intervals from 28 weeks until 36 weeks, and then daily thereafter. Estriol requires healthy fetal adrenals and placenta for synthesis, and is thus a measure of fetal and placental health. If a 35% drop in the estriol occurs over two consecutive days, then delivery is usually accomplished without delay.

Fetal activity determinations consist of watching the fetal heart rate on a fetal monitor over 30 minutes and relating it to fetal activity. A good test consists of greater than six spontaneous fetal movements with accelerations of five to fifteen beats per minute associated with that movement. Good beat to beat variability should also be seen. An equivocal test is repeated within several hours. If still equivocal, or if a poor FAD is seen, then a contraction stress test is done (CST). If the CST shows late decelerations then the patient is delivered. Reactive FADs usually assure fetal well being for the next four days.

Amniocentesis is usually carried out at weekly intervals after the 36th week. If the L/S ratio is greater than 2.0, the patient is delivered. Even with an L/S ratio of 2.0, there is stilla 3% incidence of respiratory distress syndrome.[7] Synthesis of phosphotidylglycerol occurs at 37 to 38 weeks and is felt to more directly indicate the presence of surfactant. Presence of phosphotidylglycerol in the amniotic fluid is thus more reassuring than the L/S ratio. Nevertheless, a mature L/S prompts delivery as the risk of death inside the uterus is greater than the risk in the neonatal intensive care unit.

Despite these technological advances, two clinical signs remain very important: a mother's subjective assessment of decreased fetal activity and a fall in her insulin requirement. If either of these signs is present with some other test which suggests fetal jeopardy, then the patient is delivered.

Until recently, most diabetic mothers had caesarian sections. Today, caesarian sections are done when there is severe fetal jeopardy, cephalo-pelvic disproportion, macrosomia (greater than 4,000 grams), or failed induction of labor. The vaginal route is preferred when it is practical.

When vaginal delivery is attempted, two I.V. lines with Dextrose, 5%, are started; one for oxytocin infusion and the other for insulin infusion. A Foley catheter may be in place for diabetic urines and hourly to half-hourly blood sugars are obtained by standard methods and by Dextrostix. The pitocin induction is run in the usual manner with internal fetal monitoring. The insulin infusion is titrated according to blood sugar, but usually the mother needs about two units per hour during labor. Care is taken to avoid acetone in the urine by supplementary glucose as necessary. The blood sugar is rigidly controlled as close to 100 mg.% as possible. Following delivery, the insulin infusion is discontinued and the mother's blood sugar monitored every few hours thereafter. Regular and NPH insulin then can be given as

needed. Diabetic control no longer has to be rigid and higher blood sugars are tolerated for the first few days. Pre-pregnancy insulin requirements return within the next week.

The neonate meanwhile requires careful surveillance in the nursery. Blood sugars are watched and glucose given to the infant. Bilirubin, calcium and magnesium levels in the blood are watched. Signs of respiratory decompensation and blood gases are monitored. The neo-natologist searches for congenital anomalies and alerts the pediatric surgeons when indicated.

With meticulous care, the morbidity and mortality of the diabetic pregnancy can be further reduced. Careful dietary and insulin management by the local physician during the first and second trimesters are crucial. If this care cannot be given in the community, then prompt referral is indicated. The third trimester care then falls on the perinatologists and neonatologists at a level three hospital. Only with efficient 24 hour laboratories, trained personnel in high risk obstetrics and neonatology, and neonatal intensive care units can optimum care be given to mother and child.

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Juvenile Diabetes Mellitus With Somogyi Phenomenon—Concomitant Grand Mal Epilepsy—Diagnostic and Therapeutic Dilemma

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Definition

The Somogyi Phenomenon is defined as insulin induced post hypoglycemic hyperglycemia which is an important cause of poorly controlled diabetes. In addition, it is characterized by negative urine tests for sugar and ketones, followed within several hours by substantial glycosuria and variable ketonuria; wide daily fluctuations in blood glucose levels that are generally unrelated to dietary intake; periods of mild hypothermia, nocturnal sweating, night terrors and nightmares in patients with late onset hypoglycemic effects. The basic mechanism underlying the compensatory insulin resistant hyperglycemia remains unexplained. A general consensus today appears to have been partially formulated to explain the pathogenesis of the rebound hyperglycemia by implicating epinephrine and the low level of blood glucose which in turn stimulates the anterior pituitary gland to secrete growth hormone and adrenocorticotropic hormone which enhances the mobilization of free fatty acids and increases the rate of protein synthesis for renewed gluconeogenesis. The Somogyi effect usually occurs when the blood glucose level falls to below normal levels as seen in prolonged insulin reaction and the body tries to compensate by releasing into the blood, glucose from the body storage depots. This release of glucose often is not rapid enough. The liver sometimes releases too much glucose producing elevated blood and urine glucose levels. There is no positive pattern to these rebounds but they can occur six to twelve hours after several strongly positive tests for sugar. Not every insulin reaction is followed by this manifestation. The danger lies in responses to elevated blood glucose tests with too much insulin. From the point of view of practicality, the moral is to watch a series of tests rather than to overtreat in either direction. This Somogyi effect, while not uncommon, is sometimes overemphasized as a cause for poor control of diabetes when the reasons are often much simpler and more apparent.[3-31]

Case History

R.M.O. is an 18-year-old white female in whom diabetes was discovered in February of 1968 on routine urine tests, and was subsequently admitted for further evaluation and treatment of her diabetes, as well as for routine diabetic education to include foster parents.

Pertinent past history, although limited, reveal that the father was a diabetic receiving daily insulin injections, and the mother was a full-time patient in a state mental institution. Two older siblings were living and well. Prior to the onset of the juvenile diabetes, the patient had a history of petit mal and/or grand mal like seizures commencing at three years of age and recurring sporadically for several years until almost complete control was achieved with anticonvulsive medication (initially Dilantin® and Phenobarbital, subsequently Zarontin® , and finally Mysoline® given in conjunction with Dilantin® and Phenobarbital). A trial of anticonvulsive therapy had been recommended by a neurologist because of frequent atypical spikes and wave seizure discharges in the EEG, seen in all leads during resting and natural sleep. Lapses of awareness had been noted clinically in the patient.

Insulin dosage determination after initial diagnostic work up consisted of two units of regular insulin with seven units of NPH insulin, a 1300 calorie diet, and Zarontin 250 mgs. bid. for control of epileptiform disorder. The foster parents were also instructed in the use of Dextrostix® and glucagon.

Throughout ensuing years, the patient had several undeserved physical, emotional, and socioeconomic problems. These undoubtedly led to the development of accentuated symptomatology and apparent loss of control of her diabetes which progressed to the Somogyi effect with all its manifestations, relatively severe hypoglycemic episodes followed by rebound hyperglycemia. The symptomatology of both disease entities, diabetes and epilepsy, was also compounded by at least eight transfers from various foster homes through the years, caused by the patient's rejection by the foster parents, frequent temper tantrums, forced discipline with unwarranted diatribes, peer pressure and ridicule. This later can be dramatic in a pubertal or pre-adolescent youngster and may lead to bouts of depression and emotional instability. The added non-compliance with diabetic and epileptic recommendations certainly fragmented the established didactic pathways and nullified previous medical progress.

From October of 1969 until December of 1978, the patient had several bouts of grand mal seizures, and frequent episodes of ketoacidosis requiring hospitalization. On occasion, infection acted as the triggering mechanism, but usually, no valid etiological factors could be elicited. In recent years, behavior modifications under the guise of marked aggressiveness, suicidal tendencies, and the personal feeling of sexual unattractiveness began to surface. These became evident to peers, foster parents, teachers, nursing personnel, social workers and myself. From June of 1978, nocturnal seizures became more frequent and intense. Her behavior also became more erratic and the apparent "brittleness" of her diabetic condition was almost uncontrollable because of frequent bouts of hypoglycemia, rebound hyperglycemia, daily glycosuria, and intermittent ketonuria. Blood sugar determinations were apt to vary between 68 mgs% and 530 mgs%. The patient was also gaining weight, appeared more hirsutic, and had the appearance of a patient developing the Cushingoid syndrome.

Because of the metabolic and neurological complexities, the patient was referred to Maine Medical Center, Portland, for complete re-evaluation. Daily insulin maintenance at the time of transfer consisted of 58 units NPH insulin given in the a.m. with 10 units of regular insulin as well as 10 units of regular insulin given hs. For control of the epileptiform disorder, the patient was taking Dilantin 100 mgs. a.m. with 200 mgs. hs., along with Tridione® 150 mgs. tid.

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Hospital Course:

A. *Diabetic Problem:* The patient was initially started on 68 units of NPH insulin QAM and followed closely for urines. During a single 24-hour period, a Heparin lock was inserted and hourly or q 2 hourly blood sugars were obtained with some fluctuations. Following NPH insulin injection in the morning, the patient consistently voided urines that contained 2-5% glucose but were negative to trace for acetone. Each morning thereafter, the urine glucose dropped to approximately ¼ to ½%.

Because of the large dose of insulin, the relative refractive nature of her hyperglycemia, the obesity with occasional symptoms consistent with hypoglycemia, the Somogyi effect was thought to be a distinct possibility. Dr. George Hallett, Chief of Pediatrics, Maine Medical Center, Portland, as well as the resident and consultant staff recommended that the patient be discharged on 70 units of NPH insulin per day and planned to reduce the daily insulin requirements by at least 5% every four to ten days. Because biochemical abnormalities such as glucosuria, blood sugar and ketonuria were likely to increase during the period of decreasing insulin, it was nevertheless felt that the patient would in fact feel better and that eventually there would be adequate control of her diabetes.

B. *Epileptic Problem:* EEG performed was considered to be moderately abnormal with generalized spikes and slow wave discharges compatible with primary generalized epilepsy. Dr. Walter Allen, Pediatric Neurologist, recommended that Dilantin be given at a dosage of 100 mgs. qam with 200 mgs. hs., Tridione 150 mgs. tid. and Phenobarbital 30 mgs. qam with 60 mgs. hs.

From January of 1979 until August of 1979, the NPH insulin requirements were gradually decreased from 70 units per day to 41 units per day at this writing. The patient has been placed in a new foster home with very good emotional adjustment. She has had no evidence of ketoacidosis, seizure disorders, or recurrent bouts of hypoglycemia with rebound hyperglycemia and routine blood sugars have been relatively consistent varying between 150 mgs% and 220 mgs%. The present case report demonstrates the classic Somogyi effect in a patient with concomitant grand mal epilepsy.

Comments, Discussion, With Historical Review and Perspectives

Unstable or difficult to control diabetes presents special and serious problems from the diagnostic and therapeutic point of view. It usually manifests itself in excessive variability of blood and urine glucose levels despite attempts at consistent treatment.[28] Juvenile onset diabetes usually tends to be unstable, while maturity onset diabetes usually tends to be quite stable, but there are always exceptions. Also, there are in clinical practice, varying degrees of diabetic stability and instability. One of the most troublesome, diagnostically and therapeutically challenging is the Somogyi Phenomenon or effect, characterized by recurrent bouts of moderately severe hypoglycemia followed by rebound hyperglycemia which at times may last several hours.

When insulin therapy was still in the very early stages of development in the 1930's, Dr. Michael Somogyi noted that in a certain number of patients, too much insulin could produce hyperglycemia. To him, this was a rebounding glucose level that occurred in response to insulin induced hypoglycemia, which at times was so mild that it would go unnoticed by the patient. It resulted from the body's remarkable ability to mobilize itself in times of stress for the purpose of attempting to maintain homeostasis. In over-reacting the body would increase its blood glucose to the point of hyperglycemia. Ordinarily, in most normal and diabetic subjects, the glucose will eventually level off. In some diabetic patients, the insulin induced hyperglycemia is associated with a strong antagonism to insulin, which, seemingly, can only be overcome by more insulin. This action leads to a physiologic "roller coaster" effect.

Biochemically induced processes make their appearance with insulin induced hypoglycemia when the blood glucose level falls below 50% of the pre-insulin level within a time frame of only minutes. The condition usually stimulates the release of epinephrine and catecholamines. Subsequently, the epinephrine and low level of blood glucose stimulate the release of glucagon by the pancreatic alpha cells. Glucagon and epinephrine in turn, activate enzymes and deplete the liver supply of stored glucose and mobilize fatty acids for use in making new glucose or for a cellular energy substitute.[15]

Epinephrine and the low level of blood glucose also stimulate the anterior pituitary gland to secrete growth hormone and ACTH. (There are cases in the literature where the Somogyi effect has been described in patients with hypopituitarism). As a continuing reaction, growth hormone enhances the mobilization of free fatty acids and increase the rate of protein synthesis for use in making new glucose through the known process of gluconeogenesis. ACTH stimulates the adrenal cortex to secrete corticosteroids (cortisol and glucocorticoids) which increase enzyme activity in the liver for making new glucose from proteins. Furthermore, epinephrine, ACTH, cortisol, glucagon, and growth hormone conserve glucose for vital nutrition by inhibiting glucose use in peripheral cells.[16]

Dr. Arlan Rosenbloom, Professor of Pediatrics, Division of Genetics, Endocrinology and Metabolism, University of Florida College of Medicine, Gainesville, summarized the goals of long-term self management of diabetes by stating that these goals should be realistic and attainable. The prepubertal, pre-adolescent and adolescent patients with diabetes are often given a number of strict rules that they are unable to follow, make them guilty, and rebellious, and may force them to neglect the real imperatives of self management thus leading to increasing dependency and depression. The long-term goals should be as follows: Normal physical growth and development, normal emotional development, minimal glycosuria, overt or inapparent hypoglycemia, no diabetic associated school or work absence, no manipulative use of the diabetes by the parents or foster parents, active participation of the patient in management, and thorough education of parents, families and communities.

Diagnostically, there should be comparison of urine glucose determinations and blood glucose concentrations to establish the extent of insulin administration as urine glucose does not usually reflect accurately blood glucose.

Profound psychologic implications arise with a strict diet. It now appears that the nonstrict diet approach works more successfully and is unquestion-

ably more practical for a patient who wants to maintain peer equality. The nutritional needs are the same as with nondiabetics. The diet should be flexible and simple for concentrated sweets and relatively low in cholesterol. It should have adequate amounts of unsaturated fats, relative to saturated fats.[14]

Therapeutically, only intermediate acting insulin (NPH or Lente), should be given unless there is evidence of inadequate handling of glucose. There is absolutely no need for routine mixing of NPH or Lente with short acting forms of insulin.

Overtreatment with insulin often leads to the Somogyi effect and is one of the most common errors in the management of a diabetic. This is seen in small rural hospitals as well as in large urban hospitals. Situations that lead to overtreatment are fixation on a simple mode of insulin administration, reliance on urine tests for daily insulin adjustments, inconsistent approach to prompt treatment of infections, failure to appreciate the role of emotional factors, too frequent checking of blood glucose determinations, and the attitude that control of diabetes means aglycosuria.[9]

The most common signs and symptoms of overtreatment include the following: Obvious hypoglycemia, parodoxic polyuria, nocturia, or enuresis, excessive appetite and constant hunger associated with weight gain, headaches, hepatomegaly, overnight fluctuation in urine glucose, high fasting blood sugar from overnight rebound, frequent ketosis or ketoacidosis, mood swings and irritability, exercise intolerance, absence of rationale of insulin dosage increase, ketonuria with glucosuria, weakness and dizzy spells, decreased school performance, nightmares, night terrors or night sweats, probably due to the catecholamine surge, growth failure and maturational delay, abdominal pain and constipation, weight loss, visual disturbances, and edema of the extremities.

In order to achieve the best glycemic control without Somogyizing, insulin dosage should be reduced to the pre-overtreatment level and not more than 0.6 to 0.7 units/kg/day should be given. NPH or Lente insulin should be administered if a mix had previously been given and further reduction of insulin should be accomplished in decrements of 10-20% at 4-10 days intervals.

The physician working with diabetic children must remember that he is dealing with a child or adolescent whose self concept has been seriously jeopardized by the presence of mysterious and terrifying illness. What makes it more frightening is that it cannot be seen but it can be sensed.[1] For years, young people have been telling us that when they have a high blood sugar from eating too much, they have symptoms of headache, dizziness, weakness etc; symptoms that actually sound suspicious of hypoglycemia, and tend to occur with exercise. It is now recognized that the symptoms really are due to hypoglycemia, and with the rebound effect, results in a post hypoglycemic glucosuric tide. Often there is also a ketonuric tide as well, and because the hyperglycemic phase is one of autonomic shock, urine is only obtained in the rebound phase when there is hyperglycosuria and perhaps ketonuria. In this way, the symptoms are often erroneously attributed to the high blood sugar and the apparently irresponsible youngster.[14]

Historically, Somogyi emphasized that considerable metabolic perturbations could result from symptomless mild degrees of hypoglycemia, and he was convinced that the population of insulin treated patients with inapparent instability must be much greater than the existing estimates of 10%. The phenomenon of posthypoglycemic hyperglycemia had been recognized from the early start of insulin therapy. Its mechanism via the adrenal response was implicated by animal studies done as early as 1924.

Brook and McGillivy and Dr. Rosenbloom reported similar concentration difficulties, peer underestimation, weakness, headaches, ravenous appetite with fluctuations in glucosuria and ketonuria and difficulty in identifying the problem by routine measures. They further documented that the hypoglycemic phase could be so brief as to be missed by even hourly glucose determinations or could last as long as a day, and that the insulin resistant hyperglycemic phase could last as long as a week.

Baker and his colleagues have shown the impact of emotional arousal via the catecholamine release cycle. The major contribution of psychological disturbances to the development of overinsulinism can usually be recognized in one-quarter of overtreated patients.

In recent months, physicians caring for diabetic patients have quickly recognized the value of the glycohemoglobin (GHB) determination test, a new and reliable index of long-term blood glucose control. The glycohemoglobins may be regarded as hemoglobin fixed blood glucose. They are definite compounds of hemoglobin and a glucose derivative, formed and accumulated within the living red cells. Glycohemoglobin levels correspond to time averaged blood glucose concentrations over the red cell's 120 day life span, not transient values changing hourly. Glycohemoglobin levels are unaffected by recent food intake, exercise, or even recently administered antidiabetic drugs. They represent a completely new and very useful means of monitoring diabetic patients. Poorly controlled diabetics may possess two to three times normal levels of glycohemoglobins. In response to proper therapy, these gradually decrease to normal values, roughly 7-9% of total hemoglobins.[32-7]

The American Diabetic Association states that the therapeutic goal in caring for diabetic patients should be the relative normalization of blood glucose levels. If normalization can be maintained it is believed that the onset of long-term complications of diabetes such as neuropathy, retinopathy, nephropathy, and atherosclerosis, be prevented or postponed. It has also been noted that tightly controlled diabetic patients usually feel better, have fewer infections, have more normal lipid metabolism, and lack symptoms such as polyuria, nocturia, polydipsia and polyphagia. Up

until now no practical test existed to accurately and objectively evaluate long-term blood glucose control. Glycohemoglobin levels reflect the patient's mean blood glucose concentration for the preceding weeks. Short-term fluctuation in blood glucose concentrations do not influence glycohemoglobin levels, whereas blood glucose changes lasting more than several weeks are reflected.[32]

Conclusion

Establishment of the value of tight control in juvenile diabetes has been difficult as there has never been a juvenile diabetic who is well controlled. Consequently, what we have had to deal with is varying degrees of poor control.[2] Would you ever expect insulin to raise glucose levels? No? Neither would a diabetic. Therein lies the difficulty with the Somogyi effect. It is hard to recognize and even more difficult to control.[15] Today's physician should be alert for this effect and should be able to successfully manage the problem.

With an ever growing body of knowledge as to the etiology, pathogenesis, and treatment of this metabolic disorders, diabetes researchers in the U.S., Canada, and Europe, try to approach their work from a multidisciplinary perspective usually branching out into fields of biochemistry, cellular biology, pharmacology, and virology. Methods of diabetes management have definitely improved in recent years, and as investigators develop new insulin preparations, a new hormonal insulin supplement, new glucose monitoring instrument or tests such as the glycohemoglobin determination test, new surgical techniques, it is feasible that in the near future, control systems will be devised that closely resemble the normal glucose insulin system of the human body. These advances would certainly enhance our comprehension of the disease and undoubtedly ease and facilitate the burden of therapy with its ramifications now borne by the patient and his physician.[12]

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